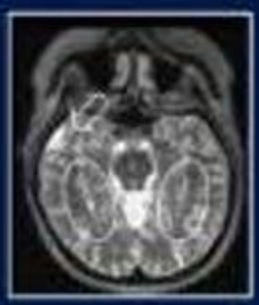
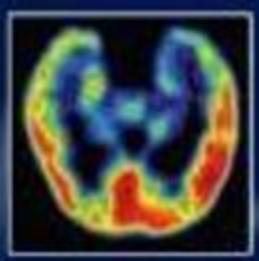
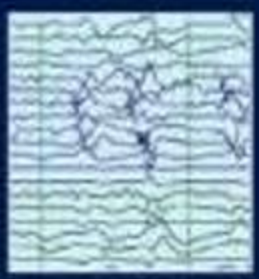
THE TREATMENT OF Epilepsy

THIRD EDITION

Edited by
Simon Shorvon, Emilio Perucca
and Jerome Engel Jr







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The Treatment of Epilepsy

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The Treatment of Epilepsy

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Section 3 – Antiepileptic Drugs

Section 4 – Presurgical Assessment and Epilepsy Surgery

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Foreword

This year the International League Against Epilepsy (ILAE) is celebrating its 100th anniversary. The celebrations will begin with the 2009 International Congress in Budapest, the place where the League held its first organizational meeting. However, epilepsy is a disease that has been with us for eons. It has been recognized by ancient cultures with detailed writings about its symptoms, causes, consequences and treatments. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits because the symptoms of epileptic seizures are not the result of the usual loss of function that accompanies many diseases that affect the brain. The powerful insights that epilepsy may provide have also been depicted in literature with specific fictional characters, such as Prince Myshkin in Dostoevsky's *The Idiot* or Simon, 'the batty boy who faints', in Golding's *Lord of the Flies*; both characters had a unique understanding of the human psyche, perhaps from the enhanced understanding that can occasionally be reached during an epileptic aura. It should be noted that epilepsy is often perceived with fear, and even in these novels it is not named. Thus, in *Lord of the Flies*, Golding tells us that Simon had 'one of his times' rather than using the word 'seizure'. Prince Myshkin was extremely frightened whenever the aura would begin because he was dreading the actual convulsive seizure. Indeed, epilepsy can be a debilitating disorder with long-lasting consequences for the person's life in terms of development, education, employment and family life. This is the reason that all of us involved in the care of patients with epilepsy are working to elucidate its secrets, eliminate the stigma with which it is wrongly associated and, most importantly, develop new effective treatments to cure epilepsy without any side-effects.

Over the past two centuries, there have been many discoveries with the advent of astute clinical observations, the development of the EEG and imaging techniques and the explosion of genetics and epigenetics. In addition, much has been accomplished with the detailed analysis of the epileptic substrate in basic studies. These studies have created the foundation on how to develop novel treatments that may deal with specific seizure disorders and syndromes. The explosion of knowledge in synaptic physiology as well as in the outputs of brain circuits (systems) has allowed the discoveries of novel treatments that may be age- or sex-specific for a particular aspect of epilepsy, that is seizurogenesis, epileptogenesis or the appearance of the epileptic state. There are insights on the role of specific neurotransmitters, inflammation, breakdown of blood–brain barrier as well as the presence or absence of a variety of malformations or lesions. New research has also advanced the understanding of the mechanisms involved not only in the initiation of the epileptic discharge, but also in how the epileptic discharge actually stop. These advances have undoubtedly led to the targeting of therapies and even to the prevention of epileptogenesis in certain animal models, although this may still be an elusive goal for our patients. Through the geometric increase of scientific data acquisition, we can also begin to understand that different factors may be involved for each type of the process that can be modulated or even reversed by specific treatments.

The third edition of this volume edited by Shorvon and colleagues is an attestation of the progress we have made as a medical community regarding epilepsy. The huge expansion of knowledge is encapsulated with state-of-the-art reviews that cover most of the currently available treatments and modalities. The editors have chosen the topics and authors well. The 85 chapters of the textbook encompass the principles of medical management, old and new antiepileptic drugs as well surgical approaches.

I am therefore extremely honoured to present the third edition. Undoubtedly, it will be an extremely important addition to our efforts to educate people on how to best utilize current and perhaps future modalities to treat epilepsy. It is also fitting that this outstanding volume will be published during the centennial year of the ILAE. It has been customary that the presidents of the League write a foreword for each edition, and I am very pleased to do so during the centennial presidency that will begin in 2009. With chapters from nearly 100 countries, the ILAE is the recognized society of medical and allied health professionals sharing the goal of improving the lives of people with epilepsy throughout the world. To accomplish this goal, we have mobilized international teams that promote education, training and research as well as the promulgation of the new treatments. Many of the contributors in this textbook have been active members of the League, who have made significant contributions in the past and will continue to in the future. ILAE guidelines and consensus statements, such as the classification of seizures and epilepsy syndromes and standards for optimal diagnosis and care for persons with epilepsy, are respected and applied around the world. The ILAE has also helped to bring epilepsy 'out of the shadows' through the Global Campaign Against Epilepsy. This important partnership between the ILAE, World Health Organization and the International Bureau for Epilepsy (IBE) has helped to identify medical and financial resources available for epilepsy care by geographic region, determine areas of treatment gaps, and raise awareness and reduce social barriers for individuals with epilepsy so that everyone will have access to effective, almost tailored treatments derived from the wealth of scientific data that our community has developed. Together we can hope that we will identify ways to improve the treatment of patients with epilepsy, determine areas of treatment gaps, and improve the livelihood of all individuals with epilepsy.

Solomon L. Moshé
2009

Preface to the Third Edition

It is 5 years now since the second edition of this book (2004) was published and 13 since the first (1996). A new edition is necessary and timely. The choices available for the treatment of epilepsy have continued to broaden, the knowledge base has grown strikingly in many areas, and updates are needed on existing treatment as well as new therapies, both medical and surgical. Increasing choice brings with it increasing complexity, and the information required to provide best practice has also probably never been greater. It is in response to this complexity that this edition is conceived.

The book has changed in many ways. First, the editorial team has been altered. Professor Ed Dodson has stood down as third editor because of the onerous nature of his administrative duties in his role as Associate Vice Chancellor and Associate Dean for Admissions at Washington University School of Medicine, and both readers and editors will miss his valuable insights and contributions so evident in the previous edition. In his place, it is a pleasure to welcome Jerome (Pete) Engel Jr, who is, of course, one of the outstanding epileptologists of our times, an enormously experienced editor and a worthy successor. Pete brings a great deal of wisdom and expertise to this edition, for which the other editors are enormously grateful. The number of chapters has also increased, from 63 in the first edition, to 74 in the second and to 85 in this edition. There are 26 completely new chapters, as well as extensive updating of the others. Also welcomed to the team are 90 new authors, joining the 53 who contributed to both this and the previous edition. The new chapters reflect the significant changes which have been made to the principles of, and approaches to, epilepsy therapy, the introduction of new drugs and the development of new surgical techniques. These changes give the book a new freshness of approach, which it is hoped will find favour with our readers.

In other ways, though, the book has not changed. The underpinning structure and principles which guided previous editions have not been tampered with. The division into four sections is retained, but the first is more focused on therapy and the practical aspects of therapy. As before, the editing has been heavy, and this has been particularly so in the pharmacological chapters to provide more uniformity, and in doing so has minimised overlap and repetition as far as this is possible. The use of summary tables is also retained, especially in the pharmacological section, in order to present data for easy reference.

Both the writing and editing have been massive tasks, and an enormous debt of gratitude is owed to all our authors for their timeliness and great forbearance in the face of numerous examples of idiosyncrasy and nit-picking by the editors in their editing work; the email traffic between all has been at times overwhelming, and one wonders how such multi-authored books were possible to fashion in the pre-electronic age. Indeed, it is pleasing to reflect on the fact that the book was completed ahead of schedule – a rare feat in publishing – for which all concerned have reason for our gratitude. The overall purpose of the book is also unchanged, and here I thought it worthwhile reproducing what was included in the preface of the second edition:

> The primary objective is unaltered [from the first edition] – namely to provide a systematic review of the whole field of contemporary therapy in epilepsy. The emphasis is, as before, on a text that provides practical information, useful for the clinician but which is comprehensive, accurate and concisely given. We [the editors] have asked the contributors to examine the evidential basis of both conventional and experimental therapies and have attempted to cover all therapeutic options . . . It remains the basic purpose of the book to guide clinical practice and rational therapy, and to be a source of reference for clinicians at every level.

Our reviewers of the last edition were kind enough to consider that these objectives were largely met, and there is confidence that this current edition is an improvement over both its predecessors. As before, the book aims to assist any doctor treating patients with epilepsy, acting both as a practical handbook as well as a work of reference. Although large, it is intended to be organised with sufficient clarity to allow the rapid access to information required by any hands-on text. It is designed for those treating children and adults, and for both trainees and specialists in the fields of neurology, neurosurgery, neuropsychiatric and general psychiatric, paediatrics and developmental medicine, neurogenetics and neuro-rehabilitation.

One remarkable feature of modern epilepsy is the global consensus that exists on the principles of therapy. This is partly due to the fact that information and opinion spreads now more rapidly than ever throughout the world via the worldwide web (the public launch of which was only in 1991) and the electronic bibliographic indices, but much credit also should go to the International League Against Epilepsy (ILAE). This organisation celebrates it centenary this year (2009) and it is now, and has been for many years, a vital link in the dissemination of knowledge in epilepsy globally, and the upward levelling of therapy in all countries. It does this largely through its congresses and its scientific journal (*Epilepsia*), and this book is heavily dependent on both. To reach the age of 100 years is a remarkable achievement and the ILAE is indeed the oldest international subspecialist society in the field of neurology; and it is in celebration of this achievement that this edition is dedicated to the ILAE. At the time of

publication of the first edition, there were only 48 chapters in the ILAE, and now there are over 100 (a growth which exceeds even that of this book!) and a membership which exceeds 15 000. All three editors are, or have been, long-standing members of the ILAE executive and almost all of the lead authors of the chapters of our book are involved deeply in the league. Indeed, contributors to the book are from 17 countries in all five continents, reflecting the global reach. In the historical introduction to this edition, the historical survey of drug therapy in epilepsy is continued, bringing this up to the year 1989. In the previous two editions, the survey covered the years 1857–1938 and then 1938–1955. Here, the story is advanced by 35 important years to 1989, and is written from the particular perspective of the ILAE.

I must offer my sincere thanks to my two fellow editors. Both have been lead editors of previous books which have dominated epilepsy publishing, and both have utilized this previous experience and have unsurpassed skill in editing as well as epileptology. Their work has been outstanding, as will be evident to all who peruse this book. Thanks, too, are owed to the chapter authors, who have largely managed to complete the task on time and to an exceedingly high standard. Writing book chapters is important but often thankless and time-consuming, not counting towards university rankings, and yet performing a valuable function for clinicians needing rapid access to knowledge in their clinical practice. The contributors to this book have excelled in their work. The production of such a book involves not only editors and authors but also a team at the publishing end, and we have reason to be greatly thankful for the efforts of the various persons at Blackwell, now subsumed into Wiley-Blackwell. The team was led by Martin Sugden, his colleague Rebecca Huxley from Wiley-Blackwell; and Catriona Vernal, the production editor, from Prepress Projects Ltd. It has been a pleasure to work with each and their expertise has been exceptional. Rebecca Huxley was also involved in the second edition, and it is a tribute to her patience that she allowed herself to be dragged again into the world of epilepsy, and yet to provide a life-raft for editors and contributors drowning in and buffeted by the heavy undercurrents of their task. The final thanks go to my patients, and those of the other contributors. Clinical practice is very much a partnership between the clinician and patient, and an understanding of epilepsy and of its treatment can be gained best by listening to those to whom we offer treatment. It is to be hoped that this book will reflect back the experience and knowledge gained in this process and result in better practice and improved therapy.

Simon Shorvon, for the editors
London, 2009

Preface to the First Edition

Epilepsy is one of the oldest recorded diseases. Throughout its history strange and varied methods of therapy have been employed. Medicaments, potions, ointments, amulets, enemas, exorcism, magic, spiritualism, magnetism, galvanism, dietary regimens, surgical and physical and moral and behavioural therapies have all been popular; reputations have been made (less often broken) and are still being made by therapeutic manoeuvres, yet none has provided the cure. Within this compass have been some effective therapies but others which are ill-directed, useless, misleading, and at times frankly fraudulent. Epilepsy is, of course, a difficult taskmaster for the inquisitive. Its fluctuating nature, its ready influence by environmental factors, its easy confusion with hysterical disorders, its multifactorial causation and its tendency to spontaneous remission, all render judgements of treatment difficult. Such confounding factors allowed ineffective and fashionable therapies to flourish in the past, and today marketing and commercial pressures add to the difficulties of evaluation.

This book is an attempt to catalogue the contemporary treatment of epilepsy in the late 1990s, both medical and surgical, in a comprehensive, concise, balanced and practical manner. Each chapter has been commissioned from an acknowledged authority, known personally to the editors as knowledgeable, intellectually honest and capable of clear communication. We have covered all matters of importance to those treating patients with epilepsy, and provide clear clinical advice on these issues. We have avoided unsupported speculation and highly biased opinion, but have asked our contributors to be as up-to-date as is compatible with our evidence-based exigencies. These are difficult and challenging requirements, which, I hope, have been largely realized.

What are the boundaries of the volume? When bromide was introduced in 1857, a new era can be said to have been entered, with a treatment that was indubitably effective. Ironically, one can note that similar claims had been made many times before in earlier and less competitive times, and the single most important lesson of history is surely scepticism. In our historical chapter, we have surveyed treatment from the time of the introduction of bromides to the outbreak of World War II, a fascinating period which provides the context for today's therapeutic approaches. From about 1940 onwards, more scientific methods were adopted to devise and assess therapy, and more rigid standards were set for proof of effectiveness. Various new therapies were introduced, but most have not stood the test of time. Even as recently as 1970, the orthodox practitioner in most countries could still offer only phenytoin and phenobarbitone as effective options for most epileptic patients.

There has been, however, in the past decade or so, a sea change, almost a revolution in the field, and a wide range of highly effective new therapeutic possibilities has become available. Not only has a series of new medicaments been introduced, but new approaches to drug therapy have become possible, and also with improvements in the investigation of epilepsy, much more effective and ambitious surgical treatment. This expansion in the options for effective treatment, both medical and surgical, is enormously welcome, but brings its own problems. The physician now has to make much more difficult decisions about treatment because of the greater range of therapeutic choices and also because the evidence on which to base rational therapy is more complex, at times contradictory, and not all readily accessible. In this book we have addressed these issues.

Our principal objective is to provide a systematic review of the whole field of contemporary therapy. We have included individual chapters on all licensed medications, on drugs in an advanced stage of clinical trial, on all specific surgical therapies of value in epilepsy, and also chapters on treatment in specific clinical situations. The contributors were asked to examine the evidential basis of both conventional and experimental therapies, and to provide a clear assessment of this. We have attempted, therefore, to encompass all therapeutic options, and their relative values in the varied clinical circumstances of the person with epilepsy. In this sense, the book should be a useful platform for all doctors treating epilepsy. Although the book is primarily about the treatment of epilepsy, we have also included an initial section of six chapters, the purpose of which is to place therapy in context. In these chapters we have also highlighted those areas in which rapid advances are being made, for herein will the context of treatment also change (the chapters on pathophysiology, the developmental basis of epilepsy, diagnosis and prognosis, and on economic cost, for example).

The information contained within the pages of this book is sufficiently comprehensive to act as a reference for specialists, and concise enough for more general clinical usage. It is very much a hands-on text, and, we hope, a constant companion. The aim of the book is to guide clinical practice and rational therapy and to be a source of reference. It has been designed for doctors in adult and paediatric medicine, both generalists and also specialists in the fields of neurology, neurosurgery, psychiatry, paediatrics, alienist medicine and in learning difficulty. It will also appeal to practitioners of the paramedical specialties who are involved in the management of epilepsy.

One remarkable fact about modern epileptology is its internationalism. In countries all around the world, the same issues about the treatment of epilepsy arise, the same therapeutic questions are debated, and there is a large and surprising measure of agreement on specific points. The international nature of epilepsy

is in no small part due to the endeavours of the International League Against Epilepsy (ILAE) which has chapters now in 48 countries and nearly 10 000 members, and whose meetings are a forum for the dissemination of information about epilepsy and its treatment. The influence of the league has left no area of epilepsy untouched. We are therefore greatly honoured, in this book, to Dr E.H. Reynolds, the current president of the ILAE, for contributing a foreword. A distinguished and accomplished physician, Dr Reynolds is also a mentor and a friend, and a person whose influence on modern British and international epileptology has been benevolent and all-embracing. Our contributors are from four continents and provide a truly international perspective. Almost all are active in the ILAE, and the text reflects to a great extent the current interest and research of ILAE members. Matching this internationalism, nearly half of the chapters are by contributors (from various countries and continents) whose training was partly at the National Hospital for Neurology and Neurosurgery at Queen Square in London. Our preliminary historical chapter looks at the history of epilepsy therapy (from 1857 to 1939) using the National Hospital as an historical mirror, and as epilepsy is still an important area of contemporary neurology at Queen Square, subsequent chapters also reflect current practice at the National Hospital. This is another thread which runs through the book and gives to the volume, at least in part, a specific flavour which I hope provides the text with an interesting perspective.

A book of 63 chapters will always pose a challenge for its editors and its publisher. In this volume, we have heavily edited some individual contributions, and worked assiduously in conjunction with the authors to avoid repetition or overlap. Where overlap has been permitted between chapters, this is because individual authors have taken differing (and occasionally conflicting) approaches which are, in the editors' view, sufficiently instructive to allow inclusion. We have also added editorial tables in places to ease comprehension and in particular to make the information contained in the text easy to follow and readily accessible to the reader, often a busy clinician. Also, we have tried to provide a uniform style, and a high quality of writing. To assemble chapters on such a disparate subject from authorities around the world, to edit and to produce a pleasing and useful book has been a major task. In this, the editors have been expertly helped by Dr Stuart Taylor from Blackwell Science, the publishers, whose skill and expertise were the essential ingredients of the successful completion of our work. We are enormously grateful to Dr Taylor, not least for his humour and forbearance in executing (a seemingly, at times, well-chosen word) the task, also to Lorna Dickson, our production editor who has worked absolutely tirelessly on this project, and other members of the design and production team at Blackwells; they have all been pre-eminent in their work. Finally, we would like to thank the chapter authors for their outstanding contributions, their patients for providing the experience on which our current therapeutics is based, and epileptologists around the world, ILAE members and others, who have stimulated our thoughts and actions in the field of epilepsy treatment.

Every effort has been made in the preparation and editing of this book to ensure that the details given (for instance of drug dosages and pharmacokinetic values) are correct, but it is possible that errors have been overlooked. The reader is advised to refer to published information from the pharmaceutical companies and other reference works to check accuracy.

S.D. Shorvon, for the editors
London, 1996

History of the Drug Treatment of Epilepsy Between 1955 and 1989 with Special Reference to the Role of the International League Against Epilepsy (ILAE)

Simon Shorvon

In the previous two editions of this book, introductory chapters were included on the history of drug treatment of epilepsy between 1857 and 1939 and then between 1938 and 1955. The first considered the topic from the perspective of therapy at the National Hospital in London and the second was written with special reference to *Epilepsia*, the journal of the International League Against Epilepsy (ILAE). This chapter considers the next 35 years, to the beginning of 1989, a period marked by a number of major developments: carbamazepine, benzodiazepines and valproate were discovered and introduced; extraordinary advances occurred in the basic sciences of pharmacology and neurophysiology; therapeutic drug monitoring (TDM) was introduced; a series of highly influential physicians became important players in the field of epilepsy therapeutics and in the ILAE; the pharmaceutical industry rapidly expanded with concomitant rapid commercialization of the therapeutic arena; and regulation and restriction arose in parallel.

The ILAE, too, grew in this period in terms of size and importance, and began – as an organisation – to influence epilepsy practice, not least through the establishment of 'commissions', of which the most important was the Commission on Antiepileptic Drugs, and the active involvement of its leaders with drug therapy. ILAE conferences were the showplace for information about these new drugs and *Epilepsia* was increasingly the journal of first choice for publishing in this area [1]. These were also the post-war period years of plenty, characterized for most of the time by sustained economic growth and optimism; in these years, very major advances were made in epilepsy therapy, and the basic approach to therapy which evolved then remains virtually unchanged today.

All history has a perspective – and all narrative can be viewed from differing points of view. Here, I have decided to adopt broadly the perspective of the international neurological community, and in particular that of the ILAE, an organization celebrating its centenary in 2009, and which has been at the policy centre of professional affairs in epilepsy during most of the period under consideration.

Epilepsy therapy in the 1950s

A good place to start this historical consideration of these years is the two-volume textbook [2] entitled *Epilepsy and Related Disorders* written by William Lennox. Lennox was the first president of the ILAE after its re-awakening in 1937 and was also largely responsible for nursing the ILAE and its journal through the Second World War [1]. This book (Fig. 1), published in 1960 in the year of Lennox's death, and written in his typical decorative style, was the definitive American text. Like most others before him, Lennox discussed treatment under a series of headings, of which drug therapy is only one: hygienic and metabolic; drug therapy; surgical therapy; and psychotherapy. Perhaps surprisingly at this late date, hygiene had first place in Lennox's book. This category included various lifestyle issues and diet, and the recommendations were similar to those of earlier authors (e.g. Kinnear Wilson, Muskens and Turner). The metaphorical language, which Lennox so favoured, though, was more curious than most:

> The close relationship of measures that make for good health is exemplified by the fact that Hygeia, the goddess of health, was no other than the daughter of Aesculapius, the god of medicine.

In regard to diet, Lennox had no particular recommendation except for an endorsement of the ketogenic diet, but he commented:

> In spite of the proven value of the ketogenic diet, it is little used today except in certain long-established centers, such as the Mayo and Johns Hopkins Clinics and the colonies of Denmark and Holland. The reasons are obvious: effective medicines are now available, the diet is limited and distasteful to the patient, and time-consuming and expensive for the parent.

Lennox considered dehydration to be ineffective, starvation to be temporarily helpful, activity to be encouraged and convulsive therapy to have some place: 'To hold a drowning man under the water seems no more illogical than to give an epileptic a convulsant drug. Yet fire can be fought with fire, and cowpox prevents smallpox.'

The focus of this chapter is on drug therapy, and to this Lennox devoted 100 pages of his book. He offered 'fifteen suggestions that as possible guide lines lead towards successful drug therapy', all of them homespun of the type 'Treat the patient', not just his symptoms, 'Prescribe adequate dosage' and '[Watch] the waves' (the EEG). His philosophy no doubt partly reflected the complacency

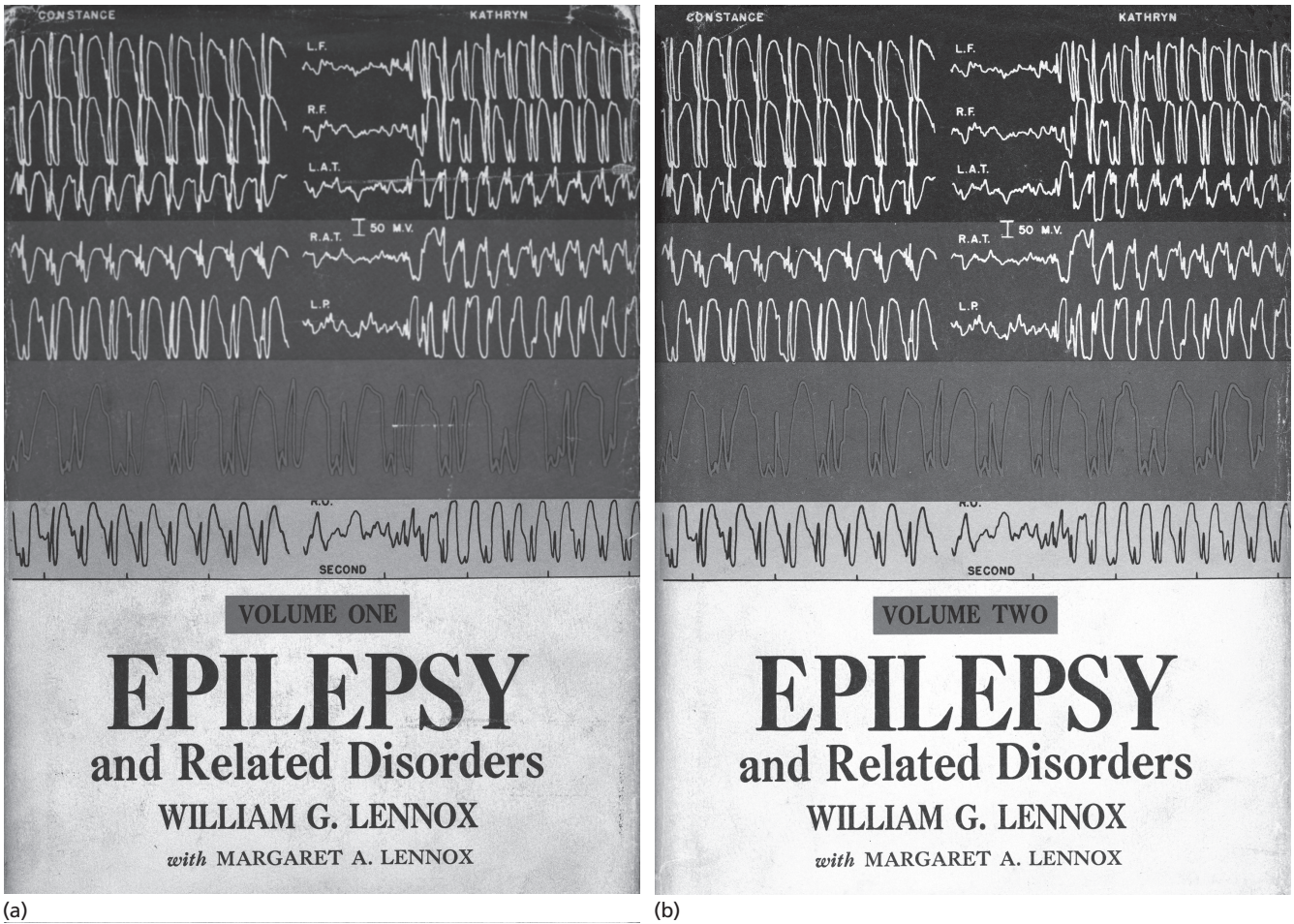

Fig. 1 The two volumes of the celebrated book by Lennox (ref. 2).

and smugness of his class, but the principles of therapy he outlined have been very influential and indeed are essentially similar to those that determine treatment today – and this despite 50 years of subsequent clinical research and a massive literature.

Lennox detailed his 'therapeutic arsenal', 16 drugs 'in use in the United States' (Table 1). The list was prefaced by a section on the question of drug-induced fatalities. Lennox wrote (strangely) that 'agranulocytosis may be an "act of God" coming or going without any explanation that man can offer'. It seems clear that drug risks concerned physicians less then than now, but this was, nevertheless, the first major epilepsy book in which drug-induced fatalities were a prominent consideration. Severe skin and blood reactions were discussed, principally in connection with mesantoin, phenurone, the diones and diamox.

At the top of Lennox's arsenal of drugs were bromides, which, owing to their side-effects and relative ineffectiveness, were 'little used today'. Barbiturates were greeted more enthusiastically. Lennox mentioned that 2500 compounds had been synthesized and of these 50 compounds marketed, of which phenobarbital was the most frequently used for epilepsy. Mephobarbital (mebaral) he pronounced 'the only barbiturate besides phenobarbital effective against epilepsy' and a drug which seemed to have more effect on 'petits' (Lennox's familiar name for petit mal). He was enthusiastic about phenytoin, especially for patients 'with long-standing convulsions previously unrelieved by phenobarbital', although Mesantoin outranked it on several points, and indeed he favoured their combined use:

> Mesantoin and Dilantin are Damon and Pythias in respect to their suitability for joint action. Similarity of action gives a doubled therapeutic effect; the dissimilarity of their side reactions keeps these within bounds.

Ethotoin was said to be one of the 1500 compounds screened by Abbott Laboratories in the previous 8 years (presumably using the maximal electroshock method formalized by Merritt and Putnam) and although effective, was associated with a high rate of blood dyscrasia. Primidone was 'especially welcomed as a contribution from abroad' (manufactured by ICI in England). Phenacemide was

> what in athletics might be called a triple threat because, more than any other drug, it acts against each of the three main types of seizures, and especially against the most feared psychomotor seizures. However, it is also a triple threat to the patient himself because of possible effect on the marrow, the liver or the psyche.

Given a 1 in 250 chance of not surviving this treatment, he asked with no apparent sense of irony, 'Is the risk too great?'. Meth-

Table 1 Lennox's 'therapeutic arsenal'.

Non-commercial official name	Patented trade name	Possible danger to
Grand mal and psychomotor seizures		
Bromides	Bromides	
Phenobarbital[a]	Luminal	
Methobarbital	Mebaral	
Diphenylhydantoin[a]	Dilantin	
Mesantoin	Mesantoin	Blood
Ethotoin	Peganone	
Primidone[a]	Mysoline	
Phenacemide	Phenurone	Blood, liver
Methsuximide[a]	Celontin	
Acetazolamide[b]	Diamox	?Blood
Petit mal		
Trimethadione[b]	Tridione	Blood, kidney
Paramethadione[a]	Paradione	?Blood, ?kidney
Phensuximide[a]	Milontin	
Ethylmethylsuccinimide	Zarontin	
Quinacrine hydrochloride	Atabrine	
Metharbital	Gemonil	

Reproduced from ref. 2, with permission.
Phenurone and Diamox were noted to be often effective against petit mal as well, and phensuximide to be often effective against grand mal.
[a]Drugs of initial choice.
[b]Drugs of second choice.

Table 2 Annual cost of anticonvulsant drugs available in the USA in 1960 (at 2007 values).

Drug	Daily dose (mg/day)	Cost of a year's supply (US$)	Manufacturer
Bromide	4000	140	–
Celontin (methsuximide)	900	476	Parke, Davis
Dexedrine (dextro-amphetamine sulphate)	10	308	Smith, Kline and French
Diamox (acetozolamide)	1000	1225	Lederle
Dilantin (phenytoin)	400	203	Parke, Davis
Gemonil (metharbital)	400	203	Abbott
Mebaral (methobarbital)	500	343	Winthrop-Stearns
Mesantoin (mesantoin)	600	147	Sandoz
Milontin (phensuximide)	2000	644	Parke, Davis
Mysoline (primidone)	1500	992	Ayerst, McKenna and Harrison
Paradione (paramethadione)	900	462	Abbott
Peganone (ethotoin)	1500	441	Abbott
Phenobarbital	200	77	–
Phenurone (phenacemide)	1500	399	Abbott
Tridione (trimethadione)	900	399	Abbott

Data derived from ref. 2.
2007 values calculated on the basis of the change in consumer price index (CPI) between 1960 and 2007 (an approximately 70-fold rise in CPI over this period).

suximide (Celontin), useful in the treatment of petit mal, was like a 'pusher' locomotive. Acetazolamide (Diamox) was noted to 'lack . . . staying power' – in other words, tolerance. Trimethadione (Tridione)

> heads the list of drugs that are peculiarly beneficial to persons subject to petits, and less distinctly for the other members of the petit mal triad . . . World-wide acceptance of Tridione was attained more quickly than acceptance of Dilantin, [but] Tridione had no competitor.

Paramethadione (Paradione) he thought to be somewhat better than trimethadione for the treatment of petit mal but worse for grand mal. Phensuximide (Milontin), ethylmethylsuccinimide (Zarontin), quinacrine hydrochloride (Atabrine), and metharbital (Gemonil) were also mentioned briefly, as well as two combination compounds and three 'accessory preparations' and some tranquilizing drugs. Cost was an important issue for Lennox. Table 2 shows his list of the costs of drugs (to the patient in the USA) converted to current values. It is interesting to note how relatively cheap most drugs were at this time.

Therapeutic drug monitoring and the rise of pharmacokinetic study of antiepileptic drugs

The application of pharmacokinetic principles to epilepsy therapy was a most important clinical advance in the 1960s and 1970s. This was an area in which, epilepsy initially at least, was in the vanguard of other medicine specialisms, and in which ILAE officers took an active lead. The involvement of the league was indeed undoubtedly a factor in recognizing the importance of these principles in clinical epilepsy practice.

The measurement of antiepileptic drug serum levels began to be studied systematically only in the late 1950s, although the technologies had been available for some years before. This early development was methodology driven (as is almost always the case when new technologies are introduced, and as shown for instance also in EEG and neuroimaging). It was also stimulated by the regulatory requirement for pharmacological information by the pharmaceutical industry. Extensive studies of bromide, ethosuximide, phenytoin and phenobarbital were conducted initially, and within a decade or so the clinical pharmacokinetic properties of all the antiepileptic drugs – their absorption, distribution, metabolism and excretion – were quite fully documented. In the 1960s, too, the measurement of serum levels of drugs entered clinical practice, and soon, in advanced units in several countries, laboratories were routinely measuring levels (Fig. 2). Initial studies were conducted in the late 1950s and early 1960s by Fritz Buchthal (the husband of Margaret Lennox-Buchthal, the future editor of *Epilepsia*) and colleagues, who found a relationship between the blood levels of phenytoin and phenobarbital to antiepileptic effects and to central nervous system (CNS) toxicity [3–8]. The classic paper by Kutt and Penry [9] was particularly influential. These were landmark studies and spawned an enormous explosion of interest in TDM, and in pharmacokinetic studies of antiepileptic drugs. Phenytoin was of course a lucky choice, as the strong level–effect relationships and the saturation kinetics render clinical serum level measurements extremely useful. This does not apply to many other drugs, and had phenytoin not been a dominant therapy, it is possible that the whole field of TDM in epilepsy might not have flourished.

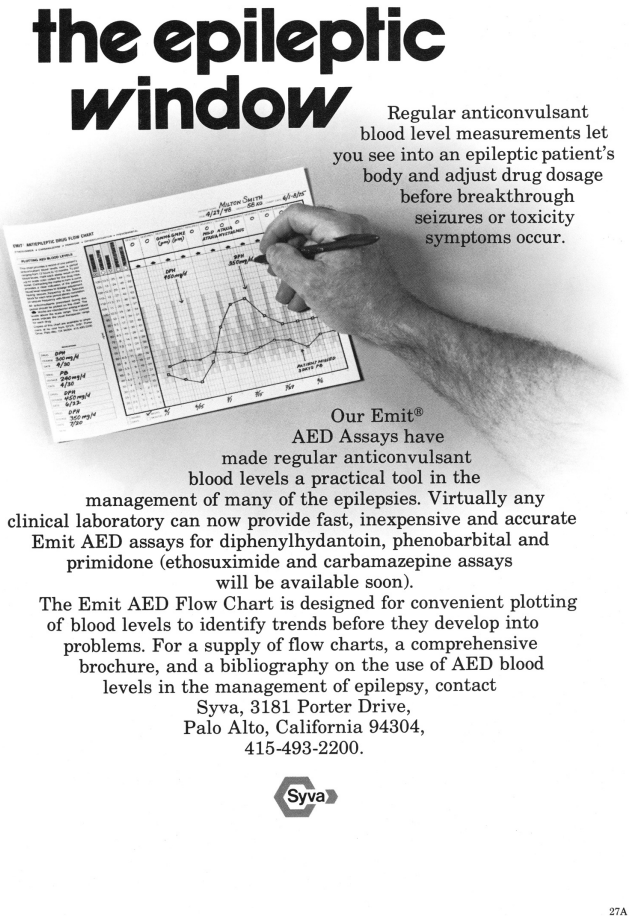

Fig. 2 An early attempt to encourage the use of serum blood level estimations.

In the late 1960s, a fairly comprehensive definition of the pharmacokinetic parameters of all the available antiepilepsy drugs had been achieved. These data were now required for registering drugs, and studies were stimulated in part by the pharmaceutical industry. During the 1970s, it also became clear that studies were needed in special populations such as children, the elderly, those with renal and hepatic disease, and in pregnancy. By the early 1980s, the characterization of the hepatic enzyme systems was largely complete, and the relevant factors, both environmental and genetic, were intensively studied.

A veritable industry has arisen related to drug interactions. This started with the study of phenytoin in the mid-1960s, and by 1972 large-scale interactions with warfarin, disulfiram, sulthiame, phenobarbital, digoxin, chloramphenicol, isoniazid, methylphenidate and chlordiazepoxide had been defined. The finding of the massive interaction between sulthiame and phenytoin also largely terminated the use of the former drug. Interaction studies have continued ever since, and although the database is progressively enlarged as new drugs are introduced, the basic principles have not changed. In the 1980s, the subgroups of the cytochrome P450 hepatic enzyme system (and to a lesser extent the UDP-glucuronosyltransferase and other systems) were characterized, and their genetic and epidemiological features explored. The regulatory agencies in the 1980s responded by requiring the pharmaceutical industry to provide more and more interaction data prior to licensing and to register data about dosage adjustments (sometimes very complex, as was the case, for instance, with lamotrigine). This not only increased the time and cost of drug development but also stimulated interest in producing drugs which avoided metabolic processes at the hepatic enzyme level. Interactions were also a major factor in the move to monotherapy in epilepsy.

In the last decade, *in vivo* testing models for determining the relevance of individual enzymes has provided a mechanism for the preclinical prediction of drug interactions. Another area of interest is that of pharmacogenomics. This has focused on drug targets, cerebral drug transporters, hepatic enzyme activity and susceptibility to idiosyncratic reactions. The work on hepatic enzymes and idiosyncrasy has been useful, but to date pharmacogenetic work on drug targets and transporters has not made discoveries of any clinical utility.

Therapy developments in the USA: the epilepsy section and epilepsy branch at the National Institutes of Health

By 1970, there was considerable disquiet in the American epilepsy community about the lack of new drugs. No drug had been licensed in the USA for 10 years, and yet there was a sizeable population of intractable patients and all the 13 contemporary drugs had side-effects which were of increasing concern. European colleagues were able to use various compounds which were not available in America, including carbamazepine, valproate, sulthiame and clonazepam. This was partly attributed to the restrictions imposed by the Kefauver–Harris amendments but also the prevalent view within the pharmaceutical industry that epilepsy 'did not need new drugs'.

In 1959, Richard Masland was appointed director of the National Institute of Neurological Diseases and Blindness (a post he held until 1968). Masland had previously been professor of neurology and psychiatry at the Bowman Gray School of Medicine at Wake Forest College in Winston-Salem and had a prior interest in epilepsy. Soon after his appointment, he decided to set up an epilepsy section, and in 1966 he recruited the young J. Kiffin Penry (Fig. 3), who had studied under Masland in Bowman Gray, to head up the section. This was a momentous decision, for over the next two decades whilst at the National Institutes of Health (NIH), Penry (later also ILAE president) led an enormous revival of epilepsy research in the USA. The epilepsy 'section' was later transmuted into a 'branch', and Penry was appointed its head and also director of the Neurological Disorders Program. In these positions, Penry spearheaded a range of activities which was without parallel. He obtained funds from the NIH administration for a multifaceted epilepsy programme. This effort was due largely to Penry's very focused vision, his energy and his extraordinary enthusiasm. He first set about reviewing current research. He realized that no company was developing antiepileptic drugs and no large-scale facility for assessing drugs existed, apart from work carried out by Goodman and Swinyard in Utah. A report was commissioned from James Coatsworth [10], which showed that current therapy was old-fashioned and inadequate. On the basis of this assessment, Penry set up the Antiepileptic Drug Development Program in 1969, which had a number of arms. Six

Fig. 3 J. Kiffin Penry, one of the most important figures in 20th-century epileptology.

'comprehensive centres' for epilepsy across the country were established to act as a focus for research and training. An ad hoc committee was created to design clinical trial protocols which would be acceptable to the Food and Drug Administration (FDA). Six drugs licensed in Europe were then evaluated in a series of controlled clinical trials, via NIH contracts, conducted at medical universities and a state hospital. On the basis of these trials, three drugs received FDA approval and were marketed (carbamazepine, 1974; clonazepam, 1975; and valproic acid, 1978. Sulthiame, albutoin and mexiletine failed to provide sufficient evidence of clinical efficacy). When Roger Porter (future ILAE secretary-general) was appointed to the epilepsy branch, he, with Penry, formed two new sections: a section on preclinical pharmacology (headed by Harvey Kupferberg) and a section on technical information (headed by Billy White). Both were to prove highly influential. In a third important development, to fill the void in preclinical anticonvulsant research and to stimulate new drug development, Penry then launched, with Kupferberg and Ewart Swinyard, a preclinical anticonvulsant screening project (ASP) in 1975 and a toxicity testing project in 1979.

The ASP was based at the University of Utah, where it remains, an enduring legacy of the Penry period at NIH [11,12]. The programme provides facilities for screening new compounds for antiepileptic drug action, at no cost, for academic medicinal chemists and the pharmaceutical industry. Within 2 years of its establishment, 1780 compounds had been tested, which originated from academic sources and the pharmaceutical industry. In these initial 2 years, 27% of compounds were shown to have antiepileptic efficacy, of which 21% were potent and 13 were thought to have potential in the treatment of human epilepsy and entered clinical trial. This programme was also set up partly in response to the belief then that the commercial value of new antiepileptics was not high enough for the pharmaceutical industry to take on the full cost. Criticisms have been levelled at the preclinical screening programme, of which the most fundamental is that the screening methods – initially only the maximal electroshock (MES) and pentylenetetrazol (PTZ) tests – will identify me-too compounds and miss compounds with novel action. (Levetiracetam, for instance, an extremely important antiepileptic drug with a novel mechanism of action, would have been discarded in the ASP screening protocol.) However, the programme continues, and 800 new compounds are tested each year, currently with an initial screening programme of MES, subcutaneous pentylenetetrazol (scPTZ) and 6 Hz psychomotor seizure tests. A total of over 22 000 compounds have been investigated since its inception. Three compounds which were initially identified in the programme have been licensed (felbamate, topiramate and lacosamide). The programme has also been involved in pharmacological work and model profiling of other compounds initially screened by the pharmaceutical company (e.g. drugs such as gabapentin, lamotrigine, levetiracetam and retigabine). Random screening is still one preferred method of drug discovery, and the relatively small number of drugs licensed from the huge number of screened compounds is an illustration of the mountain that has to be climbed.

Another very important project orchestrated by Penry and the Epilepsy Branch was the production of the book *Antiepileptic Drugs* [13], which immediately became, and has remained, the standard work on the topic, and which is now in its fifth edition. Penry had a remarkably prodigious written output, and amongst the large bibliographical projects he launched was a compilation of all published epilepsy articles extracted from the Index Medicus, another indispensible stimulus to epilepsy research [14]. On 29 July 1975, the US government established a Commission for the Control of Epilepsy and its Consequences, which in 1978 published an enormous four-volume report [15]. Penry, being an employee of NIH, was not a member of this commission, but he influenced it from outside. Numerous recommendations were made for developing epilepsy services, and this report stimulated funding and activities in the field of epilepsy for a generation. Prior to these NIH activities, epilepsy in the USA, as elsewhere, had been a rather backward subject, of little general interest. By the time Penry left NIH in 1988, there were excellent academic centres in epilepsy throughout the country.

The ILAE antiepileptic drug commission and workshops on the determination of antiepileptic drugs in body fluids

As the age of consumerism dawned in Western societies, and as the ILAE grew in stature in the late 1960s, the organization became,

Table 3 ILAE Antiepileptic Drug Commission.

1st	1971–1974	David Daly (chairman), J. Kiffin Penry, Dieter Janz, Harry Meinardi, Carlo Alberto Tassinari. Fritz Buchthal was a consultant to the Commision. This was initially known as the *Pharmacological Advisory Committee*
2nd	1974–1977	Morris Parsonage (chairman), Anthony Glazko, Mogens Lund, Ted Reynolds (secretary). Daly and Penry were active ex-officio members
3rd	1978–1981	Paolo Morselli (chairman), Mogens Dam (secretary), Rene Levy, Pierre Loiseau, F. Rubio Donnadieu (secretary-general ILAE), J. Kiffin Penry (ex-officio, president ILAE)
4th	1981–1985	Rene Levy (chairman), Lennart Gram (secretary), Paolo Morselli, Mogens Dam, Svein Johannessen, Dieter Schmidt
5th	1985–1989	Rene Levy (chairman), Mogens Dam, Lennart Gram, Hakki Hakkareinen, Paulo Morselli, Jolyon Oxley, Dieter Schmidt
6th	1989–1993	Lennart Gram (chairman), A. Baruzzi, Olivier Dulac, H.H. Frey, A.A. Gonzalez-Astiazaran, Ilo Leppik, Pierre Louseau, A. Perret (Sanofi) (with consultants for the guidelines on trials in children: C. Dravet, J. Farrell, J. Mumford, W.O. Renier, J. Roger)
7th	1993–1997	David Chadwick (chairman), Ettore Beghi, Paulo de Bittencourt, Noel Callaghan, Olivier Dulac, Lennart Gram, Tony Johnson, Dick Mattson, Franco Pisani, Roger Porter, Alan Richens, Dieter Schmidt, Cees van Donselaar

for the first time, a body which government and industry listened to in relation to epilepsy therapy. This was partly indicative of the changing social environment, but also of the outstanding quality of ILAE leadership, particularly of Penry and Fritz Dreifuss. The influence led to the recognition by industry that interaction with the ILAE could improve market share, and this changing attitude was demonstrable in concrete terms through the increasing involvement of industry in ILAE international congresses. Two ILAE activities were of particular note. The ILAE Commission on Antiepileptic Drugs (Table 3) was the one of the earliest two ILAE commissions (the other being the commission on classification and terminology, which had itself produced in 1969/70 the ILAE Classification of Seizure Type, which was to become the standard classification scheme used around the world). The commission was first set up in June 1970, under the chairmanship of David Daly, who was then the ILAE treasurer and had, at its inception, two published goals: to promote increased knowledge of currently available antiepileptic drugs and to improve the application of this knowledge in the treatment of epilepsy; and to promote development of new antiepileptic drugs with greater efficacy or equal efficacy but less toxicity than those currently available [16]. The commission was soon to be a force to be reckoned with. Its first meeting in September 1971 resulted in publication of the first edition of *Antiepileptic Drugs* [13], and a set of guidelines for the clinical testing of antiepileptic drugs followed in 1973. By 1974, it had reviewed surveys of antiepileptic drug regimens used by clinicians in France and the USA, and had held the first Symposium on Antiepileptic Drugs during the ILAE's 12th International Congress of Epilepsy in Barcelona in September 1973. Most of the Commission's work in the early years was closely aligned with that of the NIH epilepsy branch. One focus of the second term of the commission was chronic toxicity, and the chairman, Ted Reynolds, published a landmark paper on the topic [17]. The third commission modified its objectives to include information on AED use in various countries, promoting the application of ILAE guidelines to clinical trials, defining high-quality clinical centres and promoting collaborative studies. Some progress was made on all fronts, but the commission's activities did not compare with those of the Penry years. The third and fourth commissions did publish an interesting list of drug availability in developing countries – finding 'the present situation alarming' [18]. A major task of the fourth commission was to compile a glossary of antiepileptic drugs, which eventually appeared in 1991. Other guidelines were also produced [19–21]. In 1989, the fourth commission also undertook the task of updating the *Guidelines for the Clinical Evaluation of Antiepileptic Drugs*, which proved an important influence on the parameters for drug trialling by the FDA [22]. The later commissions also produced reports, but by then many bodies existed which focused on therapeutic issues, and the ILAE commission had rather lost its energy and its way.

A second ILAE initiative worth noting is the Workshops on the Determination of Antiepileptic Drugs in Body Fluids (under the rather clumsy, but memorable, acronym WODADIBOF). Between 1972 and 1979, four such workshops took place, and these helped drive the clinical chemistry agenda, at least insofar as it evolved in hospitals and universities. The topics treated included methods for quantitatively determining antiepileptic drugs; the clinical pharmacology of antiepileptic drugs; TDM; and clinical applications of antiepileptic drug monitoring. In 1972, Alan Richens started the first quality control scheme for antiepileptic drug measurements in London. The importance of this was quickly recognized, and soon Richens was providing an international service. Another workshop was set up – the Workshop on Laboratories for the Determination of Antiepileptic Drugs in Serum – which first met in New York in November 1972, but as far as I can tell was a one-off affair. A few years later, the NIH epilepsy branch, with the American Epilepsy Society, set up an Antiepileptic Drug Quality Control programme throughout the USA and Canada. This followed the model of Alan Richens and defined reliable methods and standardized procedures. The ILAE Commission on Antiepileptic Drugs was also intimately concerned with TDM and published its own guidelines in 1993, though bizarrely, the commission devoted little space to drug interactions [21].

Antiepileptic drug monotherapy

One of the most influential changes in treatment strategy – the emphasis on single-drug therapy (monotherapy) – dates from the late 1970s. This became possible with the introduction of a wider range of new effective drugs (carbamazepine and valproate) and the widespread adoption of TDM. Prior to this, combination therapy was, in effect, the norm, even for newly diagnosed patients. A survey in 1975 of 11 720 patients from 15 centres in four European countries showed that the mean number of drugs taken per patient was 3.2, of which 84% were antiepileptic drugs [23]. Furthermore, many pharmaceuticals were available in combination preparations. Reynolds, future ILAE president, and his colleagues pioneered a series of studies demonstrating that, with

appropriate use of serum level monitoring, both new patients and chronic patients were often better off with single-drug therapy [24–28]. Another factor in the previous trend to polytherapy was the poor quality of antiepileptic drug trials. Of 155 studies of carbamazepine and phenytoin reviewed in 1980, for instance, only 17% studied the drug in monotherapy, and of these none were controlled, all were of fewer than 100 patients, all were of less than 6 months' duration and none were of new patients [29].

All this was to change over the next two decades. Monotherapy became a theme in many national and international ILAE conferences and workshops, and a byword in advanced therapy. Most combination preparations of antiepileptic drugs were removed from the market. There was a marked swing to monotherapy protocols in patients with epilepsy, and the nearly universal recommendation that antiepileptic monotherapy be initiated in new patients with the disorder. By the late 1980s, the regulatory authorities had began to request monotherapy trials. Without them, a licence for a drug would be granted only for use in combination therapy. The latter requirement can be viewed rather cynically as a mechanism for restricting spending on novel drugs, for no drug that I am aware of is effective in polytherapy but not monotherapy. The requirement certainly had the effect of greatly delaying licensing of new drugs for use in monotherapy in new patients.

Monotherapy as a concept had become central to drug prescribing, and remains so (by mid-2007, the PubMed database contained over 2300 references to anticonvulsant monotherapy). Recently, and perhaps as a counter-reaction, the concept of rational polytherapy – i.e. combinations of drugs with different modes of action which might have a synergistic as opposed simply to an additive effect – has been mooted, but there is little robust clinical evidence that it is advantageous.

The treatment of epilepsy in developing countries and the concept of the epilepsy treatment gap

From its beginnings, the ILAE has shown an interest in global aspects of epilepsy therapy, but a focus on the specific problems of epilepsy in developing countries really dates only from the mid-1980s, when thereafter successive ILAE presidents showed a particular commitment to developing countries. In 1985, a landmark was the setting up of an ILAE Commission for Developing Countries. This interest reflected the more general engagement of the public in Western countries in the plight of Asia and Africa, which dates from the early 1970s and is now at the centre of political debate. Epidemiological studies of epilepsy were first carried out in the 1970s and showed that epilepsy was, as everyone always knew anyway, a universal phenomenon which respected no national or racial boundaries. Incidence and prevalence rates showed then, and have continued to show, approximately similar findings in most parts of the world albeit with a tendency to generally higher rates in developing countries and some clusters of very high rates. The higher proportion of children in populations of developing compared with developed countries meant also that the total number of people with epilepsy is highest in developing countries. Furthermore, before 1980, most of what is accepted dogma about the clinical aspects of epilepsy derived from studies done in the developed world and simply extrapolated to the situation in the developing world. This, of course, is highly inappropriate and particularly in relation to sociocultural aspects.

Table 4 The first reported treatment gap figures.

Country	Estimated numbers of people with active epilepsy[a]	Estimated number of people receiving treatment[b]	Treatment gap[c] (%)
Pakistan	450 000	22 000	94
Philippines	270 000	14 000	94
Ecuador	55 000	11 000	80

Reproduced with permission from ref. 30.
[a] Based on a prevalence of active epilepsy of 0.5%.
[b] Based on drug supply figures, minimum standard doses, monotherapy.
[c] The percentage of people not receiving therapy at any one time.

Various large-scale research projects were launched to investigate therapeutic endeavours, and some were affiliated to the ILAE. Amongst these were the studies of the International Community Based Epilepsy Research Group (ICBERG), which carried out a series of studies that were the topic of an entire session at the league's international congress in New Dehli in 1989.

The 'epilepsy treatment gap' was a term coined by Shorvon and Farmer in the ICBERG programme [30,31]. It refers to the percentage of patients in a defined population on any one day, with active epilepsy, not receiving anticonvulsant medication. The treatment gap was first calculated theoretically by dividing the figures for antiepileptic drug supply to a country by the estimated number of patients in the country with epilepsy (using an assumed prevalence of non-febrile seizures of 0.5%, monotherapy, standard anticonvulsant drug dosages and drug consumption figures based on commercial data). The method produced shocking results – such as an estimated treatment gap of 94% in Pakistan and the Philippines and 80% in Ecuador (Table 4) [30]. The one common factor in developing countries is a general lack of medical treatment available for people with epilepsy and the lack of programmes to help sufferers. This is partly because epilepsy is not a fashionable disease. But other important factors include the challenge of treating a chronic condition, lack of reliable drug supplies, cultural views of patients and the often very inadequate levels of medical manpower.

In 1997, in partnership with the International Bureau for Epilepsy (IBE) and the World Health Organization (WHO), the ILAE launched the Global Campaign Against Epilepsy (GCAE). This campaign was conceived by then ILAE president Ted Reynolds and is the culmination of ILAE interest in global epilepsy issues. A primary goal of the GCAE is to reduce the epilepsy treatment gap through community-based interventions, and to address the other problems listed above. How successful this will be is as yet not known, but a recent review of treatment gap figures suggests indeed that it may be lessening [32]. Another important output of the GCAE was an atlas of epilepsy care which was published in 2005 [33] and which provides information about resources for epilepsy care from 160 countries. The data show that there are high levels of inadequate care and large inequalities of care – with low-income countries generally faring very poorly.

As a reaction to the hegemony of modern Western pharmaceuticals, one intriguing aspect of epilepsy treatment which has been explored in the last 40 years is the value of traditional therapies still employed in all cultures. A detailed description of these is outside the scope of this paper, and some are outlandish and even ridiculous to Western eyes. But they are widely practised and adhered to. Nor is the use of alternative medicine confined to developing countries [34,35]. A recent survey of all members of the Epilepsy Federation of Arizona found that 44% had used a non-conventional treatment for their seizures at some time [27].

Antiepileptic drugs introduced into clinical practice between 1957 and 1988

During this period, a series of highly effective new drug therapies became available, some of which have endured and remain at the centre of therapeutics today (Table 5).

Ethosuximide (Zarontin®)

One of the first groups of compounds to emerge in the euphoria that followed phenytoin was the oxazolidine-diones. Trimethadione (Tridione) was one of the first, but its use was limited by unpleasant side-effects, especially hemeralopia, and occasionally exfoliative dermatitis and agranulocytosis. Miller and co-workers within the Parke-Davis Company, the manufacturers of phenytoin and indubitably then the 'epilepsy' company, systematically explored other succinimides [36,37]. Based on this work, three derivatives were identified, licensed and marketed: phensuximide (Milontin, 1953), methsuximide (Celontin, 1957) and then the ethyl derivative, ethosuximide (1958). The latter drug, α-ethyl-α-methylsuccinimide, initially studied as its laboratory name PM 671, was then given the approved name ethosuximide (or ethosuccimide) and the trade name Zarontin in 1958. The structural chemistry of all three succinimides is very similar. Ethosuximide differs from Milontin by the substitution of an ethyl in place of the phenyl group at position 3 of the basic ring structure, and from Celontin by addition of a methyl group with the phenyl group.

In the 1950s it was recognized that these minor chemical changes result in markedly different anticonvulsant spectrum and efficacy. And so it was. Celontin shows clear effectiveness in both petit mal and psychomotor seizures, but Milontin and Zarontin only in petit mal, with Zarontin far more powerful at clinically acceptable doses.

Table 5 Drugs licensed in European countries between 1957 and 1988.

1957	Ethotoin
1957	Methsuximide
1958	Ethosuximide
1960	Chlordiazepoxide
1962	Sulthiame
1963	Chlormethiazole
1963	Diazepam
1965	Carbamazepine
1967	Valproate
1968	Clonazepam
1975	Clobazam
1985	Progabide

Licensing varied from country to country and so given here is the date of first licensing or the first mention of its clinical use, in a country in Europe.

Ethosuximide acts by blocking the low-voltage T-type calcium channel, a mechanism which was identified only in 1984, some 16 years after licensing. It was investigated in animal studies first, by protecting rats against the effects of metrazol-induced seizures at a dose of 125 mg/kg. Toxicology was reported in monkeys, showing normal biochemical and haematological findings and a reasonable side-effect profile. Zimmerman and Burgemeister [38] were the first to report its effect in 109 cases of petit mal epilepsy, mixed petit mal (what we would probably now call atypical absence epilepsy in Lennox–Gastaut syndrome) and petit mal combined with other seizures. The drug was trialled at the high dose of 1750 mg/day. An 85% reduction against baseline seizure rates during a follow-up of 10–96 weeks was reported. Forty-two per cent obtained complete control, and 24% obtained 80–99% control. The drug proved much more effective in 'pure petit mal' than in mixed petit mal or in petit mal combined with other seizures (grand mal and psychomotor), an effect independent of baseline seizure frequency, and no tolerance was observed. Toxic side-effects comprised drowsiness, dizziness, nausea and gastric distress, and were reported in only nine patients. Other reports followed, which were essentially confirmatory [39–44]. Heathfield and Jewesbury [41] used doses which would be accepted as conventional today (most patients on 500–750 mg/day) and reported a more conventionally recognizable side-effect profile (34% of patients reporting apathy, depression, drowsiness, nausea, vomiting and leucopenia). All of these early authors recognized that Zarontin was superior in effect, and caused less toxicity, than the other succinimides.

Psychosis as a side-effect was first reported amongst the 60 patients studied by Lorentz de Haas and Stoel [40]. A case of Stevens–Johnson reaction was first reported in 1963 [45] and of drug-induced systemic lupus erythematosis in 1968 [46]. The first case of fatal pancytopenia was reported in 1962 [47], and it has since become clear that the drug has a propensity to cause acute and severe allergic reactions of many types.

A significant advance in the use of ethosuximide was the introduction of serum level monitoring. A rather non-specific assay was published in 1963 [48]. A gas-liquid chromatography method was published in 1965, and by 1969, a modification of this method was in routine clinical use. The relation of efficacy to serum levels was first reported in 1970 [49] in 21 patients and then by Penry and colleagues [9], who found maximum clinical control at levels of 40–80 μg/ml. Sherwin and colleagues [50] carried out a similar study and found that 93% of those controlled on ethosuximide had plasma levels above 40 μg/ml and confirmed the excellent correlation between effectiveness and plasma level. The conclusion from these studies has been repeatedly confirmed, and even today ethosuximide plasma levels remain an indispensable guide.

From about 1960, there was little disagreement amongst physicians that ethosuximide was the drug of choice for typical absence seizures, but it had limited effect on tonic–clonic seizures or atypical absence. Valproate was licensed in France in 1967 and was soon shown to be as effective as ethosuximide in controlling absence (but no more effective) and also to have a broader spectrum and to be safer. Rather surprisingly, it was not for many years that ethosuximide was replaced by valproate as drug of first choice in absence epilepsy. Perhaps this was because valproate

licensing was so delayed in the USA, or perhaps because of Parke-Davis's reputation in epilepsy. Even into the late 1980s, ethosuximide was still widely prescribed as first-choice therapy, and it has only been in the past 5 years or so that the drug was finally relegated to the far margins of conventional therapy.

Methsuximide (Celontin®)

Methsuximide, with phensuximide and ethosuximide, was discovered in the systematic exploration of the oxazolidine-diones [36,37]. The first human studies were reported in 1951 [38,51–53], and it was licensed in 1957. It was soon recognized to have effects in psychomotor as well as petit mal seizures. The drug is highly metabolized, and the active metabolite is largely *N*-desmethyl-methsuximide. The first studies of correlation between serum levels and seizure control and toxicity were published in 1972. Although the drug shows the same general toxicity profile as other succinimides, it has a much smaller risk of serious haematological or dermatological allergy, and it has continued to have a minor place in therapy, right up to the present day.

Ethotoin (Peganone®)

Ethotoin is a hydantoin drug, similar to phenytoin, and found as the result of the large screening of hydantoin drugs. Ethotoin has fewer side-effects than phenytoin, particularly in relation to the cosmetic effects of gingival hyperplasia and hirsuitism, but it is less effective, and because of its short half-life requires frequent dosing. It also, in some patients, requires high doses (up to 3000 mg/day). Although it was moderately popular when launched, it never achieved the position of phenytoin and is now only occasionally prescribed. It was manufactured by Abbott and is now available from Ovation Pharmaceuticals.

Sulthiame (Ospolot®)

This drug was produced in the laboratories of Bayer by Helferich and Kleb [54] and launched in Europe in 1962. It is a sulphanilamide drug, somewhat related to acetazolamide, and is a carbonic anhydrase inhibitor and this is probably its main mode of action. It became widely used for the treatment of partial seizures. However, a randomized clinical trial in the USA, carried out as part of the NIH initiative, was negative, and for this reason it was never licensed in America [55]. Soon after its launch, a major interaction with phenytoin was recognized, with sometimes very large rises in phenytoin levels when used in co-medication [56]. Because of this, doubts arose as to whether it had intrinsic antiepileptic action. It remained fairly commonly prescribed until the fashion for monotherapy prevailed, and the view that its efficacy was mediated largely via the interaction with phenytoin. In 1986, sulthiame was withdrawn from the market in the UK and other countries. Although licensed originally for use in partial seizures, a specific action in benign rolandic epilepsy has been suggested, and the drug was also used in West syndrome, for myoclonic seizures and for behavioural disorders. The ownership of sulthiame was transferred to Desitin in 1993 and nowadays it is sold in only a few European countries.

Carbamazepine (Tegretol®)

By the end of the Second World War, research into antiepileptic drug therapy (indeed, all drugs) was largely conducted, not as before by the universities and clinical schools, but by pharmaceutical companies (valproate is the only major exception). The rise of the pharmaceutical industry and its power and domination of the epilepsy agenda is a story as yet untold. Carbamazepine was developed in this way by the Swiss pharmaceutical firm Geigy, and was perhaps the first drug to produce large profits in the field.

Carbamazepine, initially known as G32883, was a compound first produced by Walter Schindler at Geigy in 1953 [57]. It has a tricyclic structure, similar to Tofranil, and was first investigated as a drug for depression and psychosis. Its effects on neuralgic pain were discovered by animal screening, and clinical trials confirmed its usefulness [58]. It was in fact licensed and marketed, in 1962, first for trigeminal neuralgia (although even then the blurb described it as a 'new anticonvulsant drug') (Fig. 4). Its antiepileptic effects had been investigated clinically in 1959, and first reported in 1963 by Bonduelle *et al*. [59] and Lorgé [60]. In 1964, Jongmans [61] published in *Epilepsia* a series of 70 patients treated with carbamazepine who were refractory to conventional drugs. Seventeen of 43 patients with grand mal seizures were rendered seizure free, and seven improved by more than 75%. Seven out of 24 patients with psychomotor seizures were rendered seizure free, and three improved by more than 75%. Doses of 600–2400 mg were used, and no patient was withdrawn because of side-effects. Its positive psychotropic effect was also noted. The drug rapidly gained a reputation in Europe as a very promising new antiepileptic. The first controlled trial was was undertaken at a hospital for the mentally subnormal in 1966 [62], and this was a landmark in epilepsy trial design. Tegretol was substituted for existing therapy with phenobarbital in 50% of the subjects and compared with the continuation of phenobarbital in the other 50%. Identical white tablets were produced containing phenobarbital, phenytoin, primidone and carbamazepine, and the staff and patients were blinded to which drug was being taken. The study was conducted over 18 months in 45 patients, and carbamazepine was found to have an equivalent antiepileptic action to phenobarbital, phenytoin and primidone given either separately or in combination. It was hoped that there would also be a psychotropic effect, but no difference between groups was noted. Four patients on carbamazepine died during the study, but this was felt by the investigators (one of whom worked for Geigy) to be no more than would be expected. Seven more controlled (or semi-controlled) trials were reported over the next 10 years [63–69]. In 1965, the drug was approved for use as an anticonvulsant in the UK, but approval in the USA was delayed until 1974. Its principal mechanism of action – the blockade of sodium channels – was not recognized until 1983, although earlier studies in peripheral nerves [70] had demonstrated that carbamazepine reduced sodium current in Myxicola giant axons but only at supra-maximal concentrations. The effects on repetitive firing were first demonstrated in peripheral nerves and then in cell culture of spinal cord neurons [71].

There are several important subsequent landmarks in the history of carbamazepine. With the advent of serum level monitoring around 1972, a tentative therapeutic range was set with an upper limit of 10 mg/100 ml [72]. A series of clinical trials in the 1980s established its value in monotherapy [25], but it was not until the mid-1990s that formal randomized trials in newly diagnosed patients were carried out [73,74]. Within 10 years of

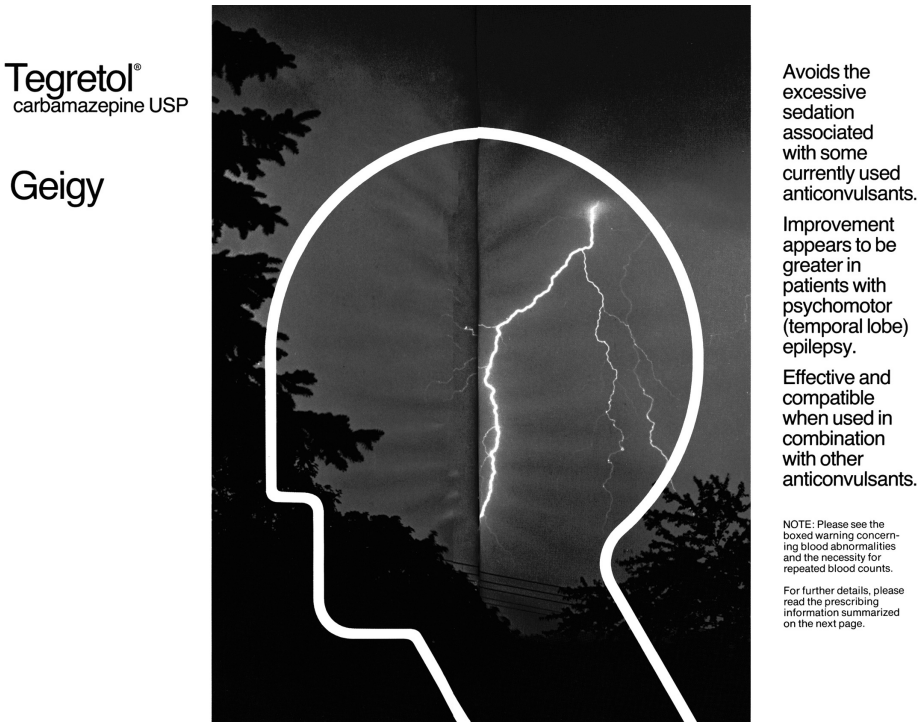

Fig. 4 One of the first advertisements for carbamazepine.

its first licensing, carbamazepine became very widely used and had, with phenytoin, become the drug of first choice in psychomotor and grand mal epilepsy. By 1965, the first reports of idiosyncratic rash, haematological toxicity and hepatic dysfunction were made, and the drug began to acquire a reputation for hypersensitivity. The rate of reactions seemed to fall after these years, and some early cases may have been due to the incipient rather than the active molecule. The rate of agranulocytosis is now known to be about 0.5 cases per 100 000 treated persons, and the rate of hepatic failure 16 per 100 000. It was not until 2004 that the strong association of Stevens–Johnson syndrome with HLA-B*1502 was noted in the Han Chinese, resulting in 2007 in an NIH advisory letter recommending human leucocyte antigen testing in all Chinese prior to starting carbamazepine [75]. The teratogenic potential of carbamazepine was recognized first in the early 1970s. In 1984, the first of several slow-release formulations was produced, but it took another decade or so for the slow-release formulations to become the preferred routine method of administration.

Most of the major characteristics of carbamazepine were identified early on, and by the late 1960s, data were available on the pharmacokinetics, carbamazepine's potential for complex drug interactions, and its common neurological and gastrointestinal side-effects (dose related). Its major routes of biotransformation were also known, but it was not until 1972 that the epoxide was recognized as a metabolite. Its central role in toxicity and the effects of drug interactions were not established until the late 1970s. Its excellent efficacy in partial and secondarily generalized epilepsy was recognized from the very first trials, as was the risk of exacerbation of absence and myoclonic seizures, and its relatively limited value in the generalized epilepsies and syndromes. Another important landmark was the introduction of slow-release formulations (which curiously differ completely in the USA and in Europe) and the recognition that many of the transient peak-dose side-effects of carbamazepine are alleviated by this formulation in a twice-daily regimen.

By the mid-1980s, carbamazepine was the most prescribed antiepileptic drug in Europe, and still is. Some 40 years after its introduction, it remains the gold standard for comparative studies of antiepileptics and the drug to beat for any new compound. By 1989, 2700 citations for carbamazepine had already appeared in the medical literature (and by 2008, 11 052) and the drug is probably the most cited and most studied compound in the history of epilepsy.

Sodium valproate and its derivatives (Epilim®, Depakine®, Depakene®)

Dipropylacetic acid (as valproate was then better known) was synthesized in 1881 and had been in use for about 80 years as an organic solvent, when in Grenoble in 1962, a small pharmaceutical company, La Laboratoire Berthier, directed by two brothers, decided to test a series of compounds in the rat for tranquillizing action. This was carried out in collaboration with George Carraz from the University of Grenoble. Dipropylacetic acid was chosen as the solvent, and when all compounds were found to be apparently antiepileptic in this model, the Meunier brothers decided to test the solvent alone. Immediately, it was obvious that the organic solvent had marked antiepileptic action. The laboratory then started to develop valproate in-house and carried out the first experimental study of the compound in 1963 in 16 rabbits given the convulsant cardiazol and protected by intraperitoneal, rectal and intravenous routes [76]. In those days, clinical testing could

Fig. 5 An early advertisement for valproate.

be started early (the thalidomide tragedy was soon going to put pay to this) and so it was with valproate. In 1964, Carraz and colleagues published the first clinical report of the effect of the sodium salt of dipropylacetic acid (sodium valproate) [77]. The drug had been initiated in November 1963 in 16 patients with largely previously intractable petit mal and grand mal epilepsy. Thirteen of the 16 cases showed marked improvement in the study, which was carried on for up to 7 months. Some patients were rendered seizure free, and the authors noted that petit mal as well as grand mal and psychomotor seizures were improved. It was soon apparent that more resources than were possible in this small laboratory were needed and the drug was sold on and licensed in the mid-1960s by Sanofi-Labaz (Fig. 5). The new company rapidly promoted the drug, and in 1967 it was approved in France and then in other European countries (Spain 1970; Belgium and Holland 1971; and Britain, Switzerland and Italy since 1972). By 1970, valproate was being widely used in Europe. The drug was not launched in the USA largely because of the lack of enthusiasm from Abbott, which held the US licence. J. Kiffin Penry, then ILAE president, then led a campaign to the US Senate seeking access to the drug. The FDA then took the unprecedented step of requiring Abbott Laboratories to supply information on valproate so it could be considered for expedited approval [78]. The battle for the approval of valproate was dramatized in a 1987 ABC television movie, *Fight for Life*, starring Jerry Lewis, in which Penry was portrayed as Dr Monroe Keith. Partly as a result of Penry's campaign, the drug was eventually licensed in 1976 in the USA, albeit initially only for the treatment of absence seizures.

The effects of valproate against absence epilepsy, myoclonic epilepsy and tonic–clonic seizures (especially when part of the syndrome of idiopathic generalized epilepsy) were well recognized by the early 1970s. In 1975, Simon and Penry published a major review of the drug that formed the basis of the subsequent FDA approval [79]. They found reports of 13 clinical trials, including two double-blind cross-over studies [80,81] and carried out what was essentially an early meta-analysis of the 10 trials which had sufficient data, in 1020 patients, and found over 50% had a reduction in tonic–clonic, myoclonic and absence seizures and about one-third of patients had a reduction in partial seizures. By the early 1970s, the effect of valproate on EEG – the abolition of photosensitivity and of spike–wave paroxysms – and the effects in atypical absence were also recognized and the pharmacokinetics fully established. The drug was rapidly gaining prominence, and increasingly being recommended as first-line therapy.

The problems which dogged the prescription of valproate thoughout this period were anxieties over its safety, and the slowness in acknowledging all aspects of valproate toxicity is rather shocking. The rather common cognitive side-effects and effects on hair were also early recognized, as was the encephalopathy (two patients in the initial trials were rendered comatose). The common effects on weight were surprisingly not recognized for many years, and even as late as 1983, Dreifuss wrote that increased appetite resulting in obesity was an 'occasional' problem. The first report of teratogenicity was by Dalens *et al*. in 1980 [82], of a dysmorphic child, and by Gomez in 1981 [83], of a neural tube defect. In 1982, the increased incidence of myelomeinigocoeles in children exposed *in utero* to valproate was described, which (15 years after licensing) established the risks of the drug in pregnancy [84]. The possibility that valproate also results in increased incidence of childhood learning disability was not reported until 2001 [85]. Hyperammonaemia was first reported in 1981 [86] and the risks of the drug in ornathine transcabamalase deficiency also in 1981. The first hepatic deaths were reported in 1978, and in 1987 these were definitively reviewed by Dreifuss, who found a risk of fatal hepatic dysfunction ranging from 1:500 in children 0–2 years old receiving valproate as polytherapy to 1:37000 in patients receiving valproate as monotherapy, with no hepatic

fatalities reported in patients above the age of 10 years receiving valproate as monotherapy [87]. The reports of pancreatitis were first published in 1979 and resulted in another review by Dreifuss and colleagues in 1993 [88]. The possibility that the drug caused polycystic ovarian syndrome and other hormonal problems was first reported in the 1990s in findings promulgated largely by a single research group and often unconfirmed by others. These risks have still not been clearly defined.

These various problems have limited the use of the drug, which is a pity given its clear efficacy. But even today, valproate remains one of the two most prescribed antiepileptic drugs (sharing the honour with carbamazepine) and a clear favourite in the idiopathic generalized epilepsies. The value of valproate was emphasized in the recent SANAD study [89]. In the generalized epilepsy arm, valproate proved superior in efficacy to both lamotrigine and topiramate, confirming its place as the drug of choice in generalized epilepsy. The old lady, it seems, can still hold her own.

1,4-Benzodiazepine drugs (chlordiazepoxide, diazepam, clonazepam)

A most significant pharmacological development of the post-war period in general psychiatry was the development of a new class of drugs, the benzodiazepines. These compounds have had a major impact on popular Western society and culture and have entered the folklore of the age (e.g. the 'little yellow pills' and 'mother's little helpers' of the famous song). They helped fuel a revolution in biological psychiatry and its social reaction, the antipsychiatry movement of the 1960s. Of course, the main impact of this class was its anti-anxiolytic and hypnotic action, but the benzodiazepines were also early recognized to have antiepileptic effects. The 'benzodiazepine story' as related by the protagonists at the time is an intriguing insight into contemporary pharmaceutical development. In 1952, the first reports of the clinical effects of chlorpromazine were published, and its obvious commercial importance and rapid success led the pharmaceutical industry into a race to discover other psychoactive drugs which might have improved properties. The Swiss pharmaceutical giant Roche was a leader in the field, and had developed a range of animal-testing models for assessing sedative properties. Leo Sternbach was a medicinal chemist in their research laboratories [90]. In the mid-1950s, he decided to investigate the pharmaceutical actions of a group of compounds he had created which came to be known as the benzodiazepines. They were attractive candidates as they were readily produced, capable of chemical manipulation to produce a whole family of compounds, largely unstudied in pharmacology and had the 'look', as he later put it, of being biologically active. He chose first to study benzheptoxdiazines and synthesized a range of these with different side-chain products. Initially, no biological action was found, and his laboratory was then asked to focus on other research areas. In cleaning up, his technician found a few hundred milligrams of some crystallized compounds which were thought to be quinazoline 3-oxides prepared in 1955. They decided to submit these for animal screening. The results were unexpectedly exciting – the drugs had powerful sedative and antiepileptic effects. Sternbach pressed on. He found first that the compounds were not in fact quinazoline oxides but had a seven-membered diazepine ring. In May 1958, a broad patent was filed for the 2-amino-1,4-benzodiazepine 4-oxides and various substituents in the benzo- and phenyl rings. It was granted in July 1959. An intensive pharmacological programme of work ensued, and one of the original compounds, given the generic name chlordiazepoxide, proved superior to its derivatives and was submitted for licensing to the FDA. In short order, in 1960, the compound was approved and licensed under the name of Librium. Sternbach then carried out further chemical exploration and discovered that the *N*-oxide function was not necessary for the pharmacological action (contrary to the then hypothesis on mechanisms of action) but that biological activity depended on the presence of a chlorine in the 7-position. With additional manipulation, another compound, given the name diazepam, was discovered and found to have a broader spectrum of activity than Librium, stronger antiepileptic and muscle relaxant properties, and very low toxicity. Following clinical studies, the drug was licensed in 1963 under the name Valium. In the next 15 years, over 4000 related compounds were synthesized and screened, and by 1978, 23 compounds had been licensed worldwide (including eight in the USA). It is instructive to note that the compounds were not produced rationally in the sense that they were designed with a specific epilepsy or anticonvulsant mechanism in mind, but initially rather randomly discovered following screening in an animal model – much as was phenytoin. However, the chemical family was then explored using systematic chemistry – with thousands of products each analysed and again screened in the same models. In this way, the basic chemical structures necessary for clinical action were elucidated. Such a programme was only possible in the research factories of the major pharmaceutical companies. The story of the benzodiazepines opened a new chapter in the history of drug development [90].

The value of these drugs in human epilepsy was rapidly recognized. The anticonvulsant effect of Librium was first reported in 1960 [91]. In 1962, a series of cases of epilepsy treated with Librium (Ro 5-0690) and Valium (Ro 5-2807) were presented by Hernandez at the second Latin American Congress on Psychiatry in Mexico and by Madalena in Brazil in 1963. Madalena also mentioned the use of clonazepam in epilepsy, which he considered superior to diazepam due to its lower dosage, almost complete absence of side-effects (an extraordinary assessment from today's perspective), better effects on the behavioural disorders associated with epilepsy, safety and more favourable efficacy in petit mal than either Valium or Librium (Fig. 6). These drugs were beginning to be widely used in epilepsy. In 1965, Henri Gastaut weighed in with a laudatory report of the use of Valium in status epilepticus [92], and 6 years later was even more enthusiastic about the new agent clonazepam (Ro 05-4023) [93,94].

In 1973, Browne and Penry [95] published a major review of the use of the benzodiazepines in the treatment of epilepsy. (Penry's colleague Ewart Swinyard had published reviews of the experimental effects in 1966 and 1969.) This review was a definitive statement on the position of these drugs after a decade of use, and its main purpose was surely to persuade the regulatory agency of the need to license these drugs, which were now widely available in Europe and elsewhere but not in the USA (Penry and colleagues had written similar reviews of carbamazepine and valproate for similar reasons – see above). The review covered clinical pharmacology and toxicology, effects on EEG and clinical

Fig. 6 An early advertisement for clonazepam – one of the first advertisements to advise the use of the drug based clearly on the modern classification of seizures.

effects, and summarized the status of the benzodiazepines 10 years after the first licensing of Valium. By then there were 28 open studies of benzodiazepines in patients with refractory petit mal and one open study of new cases – dating from 1961; Browne and Penry were scathing about the methodology, but noted that the results were uniformly encouraging. They concluded that controlled studies were needed 'to establish definitively the role of benzodiazepines in the treatment of absence attacks'. In 1977 they reported one such study, a double-blind comparison of clonazepam and ethsuximide. The drugs were reported also to be useful in photosensitive epilepsy, myoclonic epilepsy, West syndrome, akinetic seizures, alcohol withdrawal seizures and eclamptic seizures. However, the results of treatment in grand mal and focal epilepsies were generally less good, and indeed, grand mal seizures could be exacerbated. On the question of status epilepticus, Penry was more lukewarm than Gastaut had been. He reviewed 35 articles on the effectiveness of diazepam in various types of status epilepticus, but failed to mention Gastaut's article, and noted lasting control of the status in between 20% and 89% of cases, depending on the seizure type. The principle objection to diazepam was its respiratory depressant and hypotensive side-effects. Also, because of the propensity for tolerance to develop on continuous oral medication, the drugs were most useful in their parenteral formulations. It is difficult to disagree with any of the conclusions in Penry's review, which still largely apply today.

The mechanism of action of the benzodiazepines was the subject of intensive study in the 1960s and 1970s. The importance of γ-aminobutyric acid (GABA) as the main cerebral inhibitory transmitter was established by 1975, and shortly after this the main site of action of the benzodiazepines was shown to be at the GABA receptor. The benzodiazepines still used in long-term oral therapy for epilepsy now are clobazam and clonazepam, and occasionally nitrazepam and diazepam. None are currently considered first-line therapy. Only clobazam is widely used worldwide (although not licensed in the USA), and clonazepam is used extensively in France. Enthusiasm for their antiepileptic effect has been tempered by the occurrence of tolerance and the problems of dependency and sedation. Rectal diazepam, buccal and intranasal midazolam, and intravenous diazepam and lorazepam, however, are still the drugs of choice in the first-line therapy of convulsive status epilepticus and in generalized absence status epilepticus.

Clobazam (Frisium®)

Clobazam is an outsider in the benzodiazepine family. It is the only benzodiazepine which has been extensively studied clinically in which the diazepine ring is substituted by a nitrogen atom in the positions 1 and 5 of the B ring and no imine group at positions 4 and 5. It has distinctive properties which set it apart from the other benzodiazepines, and which are probably explicable by its different differential action on subtypes of the $GABA_A$ receptor. This structural change results in an 80% reduction in its anxiolytic activity and a 10-fold reduction in its sedative effects when compared with diazepam in animal studies. It has been licensed in Europe since 1975 and Canada since 1988, but is unavailable in the USA. It is widely used in specialist epilepsy clinics, where this underdog of a drug has many champions.

The antiepileptic effects were reported in mice in 1973 and then in baboons [96]. The first human trials were reported in 1979 by Gastaut and Low [97]. It has since then been the subject of at least two international conferences and is the most widely used of the benzodiazepine drugs in chronic epilepsy, at least outside the USA. It was discovered in 1984 that its main effects are due to its active metabolite, *N*-desmethylclobazam, which has a longer half-life and greater serum levels than the parent drug. Clobazam was first trialled as an anxiolytic and was licensed for this purpose, although it was withdrawn in recent years for this indication as it has few advantages over the 1,4-benzodiazepine drugs. Its antiepileptic properties were discovered a few years later when clobazam was made available, in October 1977, to the Marseilles group of Gastaut. It was tested first for a few days in 140 patients with frequent seizures, and then continued in patients who showed a response at a dose of 0.5 mg/kg/day. Its effects were dramatic initially, as has been confirmed many times since. Seventy-six per cent of the patients with severe epilepsy showed a marked and potent response, although this was maintained in only 52% after

a matter of months. Side-effects were slight, and good results were obtained in patients with all types of seizure, in reflex epilepsy and in Lennox–Gastaut syndrome. Since then, its strong antiepileptic effects have been confirmed in numerous open and also eight double-blind placebo-controlled studies carried out between 1982 and 1991, four from the UK, and one each from France, Germany and Canada and one multicentre European study (reviewed in Shorvon [98]). The study from Canada found clobazam to have equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy [99].

The major problem with clobazam, as noted immediately by Gastaut, is the propensity for tolerance to develop in 50–80% of patients, sometimes within days or weeks of its initiation. Manoeuvres such as drug holidays, initiation at very low doses, the use of partial benzodiazepine agonists and of very high doses have all failed to circumvent this problem. Other side-effects, such as drowiness, dizziness, weakness, restlessness and aggression, are either less common or less marked than with any of the 1,4-benzodiazepine drugs. It is, in routine practice, very well tolerated. Its mild anxiolytic effect is also useful in some patients with epilepsy.

It retains a special place in the therapy of chronic epilepsy and is widely used. It also has a useful role as one-off prophylactic therapy on special occasions when it is particularly important to prevent a seizure (e.g. on days of travel, interview, examinations and so on) or in catemenial epilepsy [98,100]. Its availability in Canada, but not the USA, is said to have resulted in a lucrative cross-border trade.

Progabide (Gabrene®)

As might be surmised from its name, this drug was designed as a prodrug of GABA, and was manufactured and developed by the French company Synthelo Laboratory. It was a direct product of the GABA wave (described below) of neurochemical research, and in animal studies progabide was shown to have a wide spectrum of anticonvulsant actions [101]. This was, furthermore, also one of the first drugs to be identified in the NIH Antiepileptic Drug Development (ADD) programme. Although it is a GABA prodrug, its exact mode of action is still not entirely clear. It may act at the $GABA_B$ receptor (subunit 1) and regulate the availability of functional $GABA_B$-R1A/$GABA_B$-R2 heterodimers by competing for $GABA_B$-R2 dimerization. It certainly is not a direct GABA agonist in the same way as vigabatrin. Its effectiveness is complicated by the fact that it elevates phenytoin concentrations and enhances the metabolism of carbamazepine to the epoxide. Some clinical studies showed positive effects and others were negative in both partial and absence seizures. It was also trialled in a head-to-head comparison against valproate which was terminated prematurely, as it caused elevated levels of liver enzymes and was less efficacious than valproate. There have remained persisting anxieties about its hepatic toxicity. It has been extensively studied as a drug which improves tardive dyskinesia in Parkinson's disease, although has never been licensed for this use, and has been found to have mild psychotropic effects. Progabide (a French drug) was licensed in France first in 1985, and by 1992 was reported to have been used in over 2500 persons. It is now licensed in France for use in monotherapy and also as adjunctive therapy for generalized tonic–clonic, myoclonic and partial seizures, and for Lennox–Gastaut syndrome, in both children and adults. It is not licensed in any other European country nor in the USA.

Other drugs

Corticosteroids and particularly adrenocorticotropic hormone (ACTH) were also introduced into clinical epilepsy practice in 1950. Prior to this, steroids were thought to be proconvulsant, although ACTH and cortisone were both known to normalize the EEG [102]. The first report of efficacy in childhood epilepsy was in 1950 [103] and then in 1958, when Sorel and Dusaucy-Bauloye [104] demonstrated the dramatic effect in infantile spasms. Thereafter, ACTH rapidly became, and remains, first-line therapy for this indication. ACTH and cortisone were also shown in the 1950s to have value in occasional cases of other types of childhood epilepsy and in status epilepticus. Paraldehyde became another drug widely used in status epilepticus. The first report of its anticonvulsant action was by Wechsler in 1940 [105]. Apart from its use in status epilepticus, it was also frequently helpful in alcohol withdrawal seizures. Its intravenous use in status epilepticus required a complex series of glass tubing (as it degrades plastic), had the appearance of a chemistry lesson, and is still seared in the memory. It continues to be used as a rectal instillation, particularly as out-of-hospital use in patients with severe epilepsy (e.g. in epilepsy institutions). Its undoubted safety and efficacy make it a popular choice, although few who have observed the effects of paraldehyde will forget its lingering odour, a madelaine of institutional practice. The first report of the use of chlormethiazole in status epilepticus was in 1963 [106] and a number of uncontrolled studies were reported in the next 10 years, all showing that the drug rapidly controls seizures in most patients, including those unresponsive to diazepam infusion [107]. It became a standard second-line therapy in the 1970s, especially in Britain, and I remember many cases of status treated by chlormethiazole infusions well into the 1980s. It has a tendency to accumulate dangerously though, and by 1990 was only occasionally used, as other safer alternatives entered clinical practice and protocols for the therapy of status become more standardized.

Epilepsy therapy in 1989 – the textbook *Antiepileptic Drugs*

An appreciation of contemporary advanced therapy for epilepsy in 1989 can be gained by a reading of the third edition of the textbook *Antiepileptic Drugs*, which was published in that year and which became a standard text [108]. It is clear, by comparing this and Lennox's book published some 30 years earlier, just how the introduction of carbamazepine and valproate, and to a lesser extent the benzodiazepine drugs, had made a rapid and enormous impact on epilepsy practice. By the mid-1970s, carbamazepine and valproate dominated therapy in Europe and, 10 years later, were doing the same in the USA. Their advent pretty well marked the end of all prescription of bromide, the virtual end of the routine use of phenobarbital, at least in Europe (e.g. in my own practice in 1978 this had now largely disappeared), and a marked reduction in the use of phenytoin in Europe and less so in the

USA. The rise of clinical pharmacokinetics was the second major development in this period – with most of the advances in this area made between 1960 and 1972, and by 1989 most of the major parameters relating to the absorption, distribution, metabolism, excretion and drug interactions of all drugs were fully established, as was the characterization of the P450 system (emphasizing particularly the various genetic phenotypes) and the importance (and mechanisms) of drug interactions. The first mention of teratogenicity appeared in 1968 [109]. The selection of antiepileptic drug therapy was also by this time firmly linked to seizure type, using the new ILAE classification, and indeed the therapeutic framework and approach of that time is essentially unchanged today, 20 years later.

One less obvious consequence of these changes was the much greater interest in 'epilepsy' as a subject. In most advanced neurological units, by 1910 epilepsy had fallen from its position as 'queen' of neurology to a rather peripheral subject. It remained in the doldrums at least until 1940, with a reputation as a tiresome condition (with the inference of having tiresome patients) which neither challenged the intellect nor stimulated the interest of the neurological establishment. Neurology had the reputation of being an essentially diagnostic subject which required high intelligence and a rigorous approach based on interpretation of the clinical examination. Epilepsy was not generally a diagnostic challenge, nor did the patients need a sophisticated neurological examination. The attractions of the topic, though, progressively grew in the second half of the 20th century, with the introduction of diagnostic aids, notably EEG, TDM and neuroimaging, and particularly with the introduction of novel therapy. Few neurological specialties had such a range of effective therapies. Furthermore, the establishment of specialized epilepsy units, of which the most celebrated was Lennox's Seizure Unit in Boston, was an important step in raising the profile of the disorder. Similar units opened in the 1970s and 1980s in Europe. The example of the National Hospital at Queen Square in London illustrates this point well. In 1975, for instance, there was no particular epilepsy interest, no research and no specialized clinic. Epilepsy was considered a subject of little interest, in spite of the illustrious role the institution had played in the history of epilepsy. In 1983, an epilepsy group was formed and epilepsy became progressively, again, one of the hospital's leading specialties in both clinical and research fields. This new dynamism in the field of epilepsy was partly stimulated by financial support from the pharmaceutical industry. This was a period in which Ciba-Geigy, which manufactured carbamazepine, and Sanofi-Labaz, which manufactured valproate in Europe (Epilim, Depakine), provided sponsorship in increasing quantities to many educational activities. Consequently, the ILAE conferences grew in size and ambition, and in this period the modern conference, with satellites and a commercial exhibition, was born.

The antiepileptic drug market, the rise of the pharmaceutical industry and the rise in regulation

The post-war period was marked by an enormous rise in the power and profits of the pharmaceutical industry and the intense commercialization of this therapeutic area (as of many others in medicine). Initially, this was a period of great optimism. The drugs developed in the 1950s and marketed in the 1960s included the first oral contraceptives, cortisone, antihypertensives, monoamine oxidase inhibitors, chlorpromazine, haloperidol and Valium (the latter drug becoming at one point the most prescribed drug in history). The profits of the drugs companies soared in the 1960s, and for many years; for instance, the US pharmaceutical sector was judged the most profitable of all industrial sectors in terms of rate of return (2006: 17% on revenue).

Between 1955 and 1989, a number of important antiepileptic drugs were introduced and the drug industry had come to occupy centre stage in the epilepsy world, as never before. The leadership of drug development has moved away from the university academic environment to the in-house laboratories of the companies. The research is now much more focused and more applied, and this move is probably the fundamental reason for the rapid increase in the number of compounds being brought forward for clinical testing. The move has had negative effects also, not least the fact that transparency has diminished and drug development has become more secretive. In the next 20 years, the pharmaceutical industry was to become a more ruthless commercial enterprise kept under conditions of tight secrecy to protect commercial interests. Epilepsy therapeutics has also experienced a transfer of influence away from the academic neurological community to the marketing departments of pharmaceutical companies. This latter change was first noticeable in the 1960s, and has been especially prominent in the last 10 years. The relationship between the two continues to be at the still centre of the topic.

The increasing influence and power of the pharmaceutical industry has been paralleled by, and has no doubt contributed to, an increase in governmental regulation and restriction. This reflected the growing public interest in, and concern about, drug therapy in many areas of medicine. In fact, it was a series of well-publicized debacles which led to incremental changes in governmental regulation.

The example of the legislation in the USA is instructive, although similar legislation tended to follow the American example in other countries. Prior to 1906, there was almost no regulation of drugs or medicines in the USA, which lagged behind Europe in this regard. The first major legislation was the Federal Pure Food and Drugs Act, passed by the US Congress in 1906, in response to public concern about excessive misbranding and adulteration of food. This act required, for the first time, simply 'accurate' labelling, but there was no obligation to provide any real evidence of either toxicity or efficacy. By the 1930s, the nascent consumer movement raised the awareness of the US public (if not their doctors), who became increasingly concerned about the quality of medicines. Efforts were made to tighten regulatory control, for instance through the ill-fated Tugwell bill of 1933, but such efforts never made it to the legislature, partly because of the powerful industrial lobby. However, in the 1930s, the deaths of more than 100 people caused by 'elixir of sulphanilamide', a liquid form of sulphanilamide, dissolved in diethyleneglycol, ignited public anger. In response to this, in 1938, a new act – the Food, Drug and Cosmetic Act – was passed into legislation. This required, amongst other things, evidence of safety to be submitted to the FDA prior to marketing. Between 1938 and 1962, no other major changes were made to the laws concerning drugs and medicines (although there were changes to

laws concerning foodstuffs), but that was all changed by the thalidomide tragedy. Thalidomide was a drug very widely sold during the late 1950s and early 1960s to pregnant women to alleviate morning sickness and to assist sleep. It was inadequately tested, and between 1956 and 1962, approximately 10 000 children were born with severe malformities in Europe and elsewhere (not, however, in the USA, where the drug had not been licensed). In response to the massive public outcry, new laws were drafted, and in 1962, the Drugs Amendment Act (the Kefauver–Harris amendment) was signed into law by John F. Kennedy. These amendments were a milestone in medical history, and for the first time required evidence of efficacy as well as safety of medicines, and also the continuing evaluation of drugs already on the market and the retrospective evaluation of efficacy of all drugs introduced between 1938 and 1962. The Kefauver–Harris amendment also required drug advertising to disclose accurate information about side-effects and efficacy of treatment and placed on the FDA an obligation to establish guidelines for testing all classes of drugs, including antiepileptics. A new system of licensing was devised by which the FDA required each company to obtain an IND (a notice of claimed investigational exemption for a new drug) before it was permitted to use the drug in human subjects. Complete chemical and manufacturing information, preclinical screening and animal investigation, including toxicology, teratogenicity and safety, had to be submitted to the FDA before the IND was granted. Once an IND was granted, clinical testing could begin and was divided into phase I (healthy volunteers), phase II (initial controlled studies in seizure patients) and phase III (broad and varied clinical studies). After completion of these studies, a 'New Drug Application' (NDA) could be filed. If approved, the drug could then be licensed.

These new regulations no doubt protected the public from dangerous compounds, but there were also immediate negative consequences. The cost of developing antiepileptic drugs increased greatly due to the huge increase in the number of animals and procedures needed in preclinical testing, and in the complexity and scope of this testing. Large controlled clinical trials were also required, and gone were the days when a few short open studies were sufficient (as applied, for instance, for phenytoin or ethosuximide). This led to a rapid fall-off in the number of drugs being developed, and the US companies in particular largely withdrew from the field of epilepsy, engendering considerable concern in epilepsy and ILAE circles. Responding to these concerns, in 1972 the US National Institute of Neurological Disorders and Stroke (NINDS) set up an ad hoc committee on anticonvulsant drugs to translate the new rules into practice. This body, in conjunction with the ILAE Commission on Antiepileptic Drugs and the FDA, produced a detailed document outlining the approved design, patient selection and protocols for new drug trials [110]. This new schema became the framework for drug development right up until the present day.

In the middle of the 1980s, the FDA again began to tighten its regulations in relation to antiepileptic and other drugs. This was not driven by legislation, but rather the agency itself raising the bar and initiating more scientifically valid methods of assessment. By now, epilepsy had entered the era of the randomized controlled trial (RCT), which had for some time already been introduced in other areas of medicine. In epilepsy, the FDA decided that RCTs were a necessary prerequisite of licensing. They also made the momentous decision that the new drugs had to demonstrate superiority over a comparator compound rather than equivalence, and so almost all the studies compared the new drug with placebo rather than a conventional therapy. This decision was based on the perceived difficulties of interpreting the finding of non-inferiority, but resulted in a lamentable lack of head-to-head RCTs. This decision was to have a major influence on the conduct and design of clinical trials.

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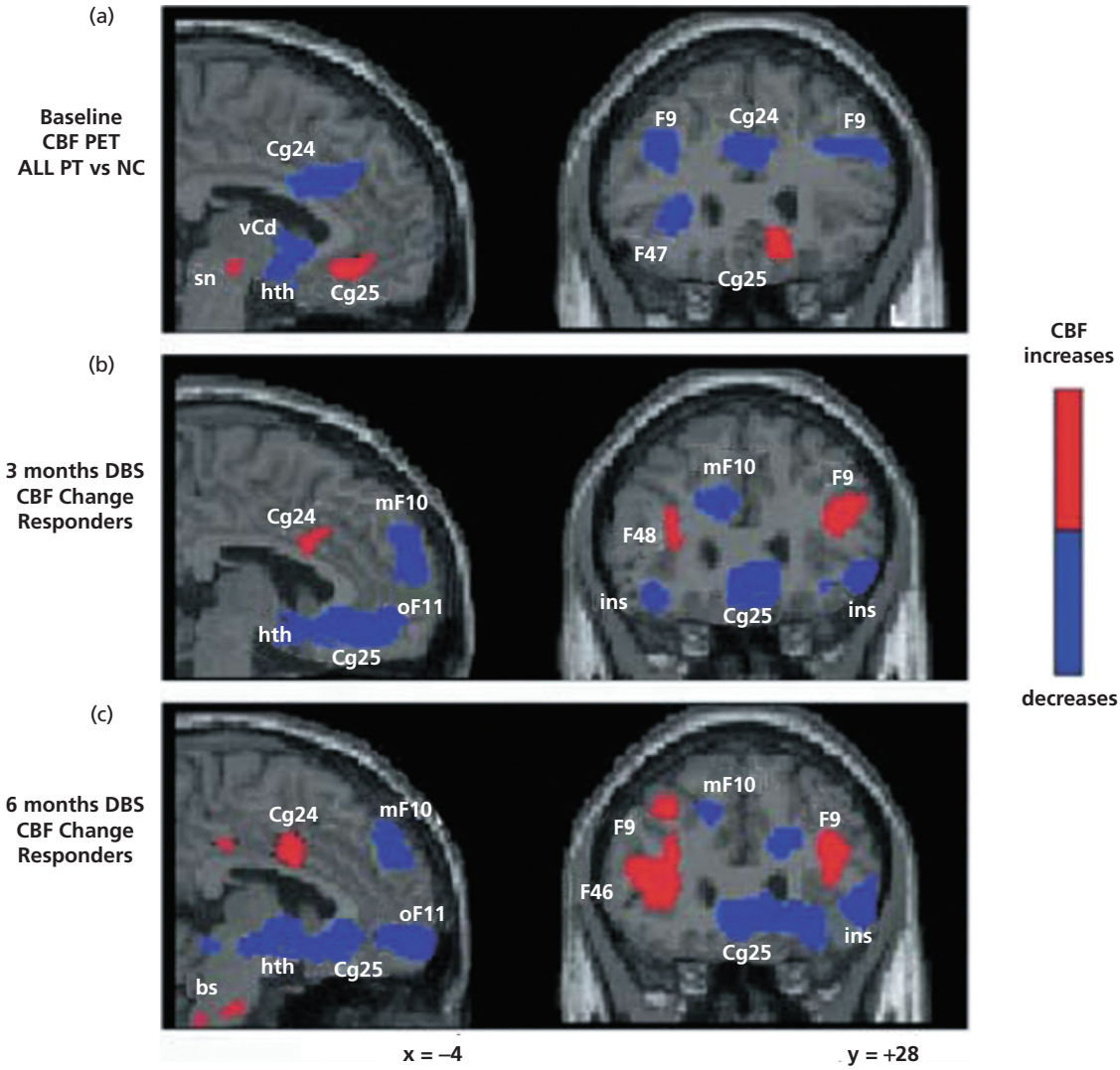

Plate 21.1 The regional cerebral blood flow (CBF) changes [positron emission tomography (PET)] in depressed patients treated with deep brain stimulation (DBS) [65]. (a) Baseline: increase in subgenual cingulate (Cg25) and decrease in dorsolateral prefrontal (F9), ventrolateral prefrontal (F47) and anterior cingulate (Cg24) cortices. (b) Three months: decrease in Cg25, hypothalamus (Hth), anterior insula (ins), medial frontal (mF10) and orbital frontal (oF11); increases in prefrontal (F9/46) and dorsal cingulate (cg24). (c) Six months: this same pattern is maintained, although additional increases are seen in the brainstem (bs). Significant CBF increases in red; decreases in blue ($P < 0.001$).

Plate 29.1 Informal taxis overloaded with people are a common form of public transportation in low-income countries. Traumatic head injuries in road traffic accidents are common (photo courtesy of Michael J. Potchen).

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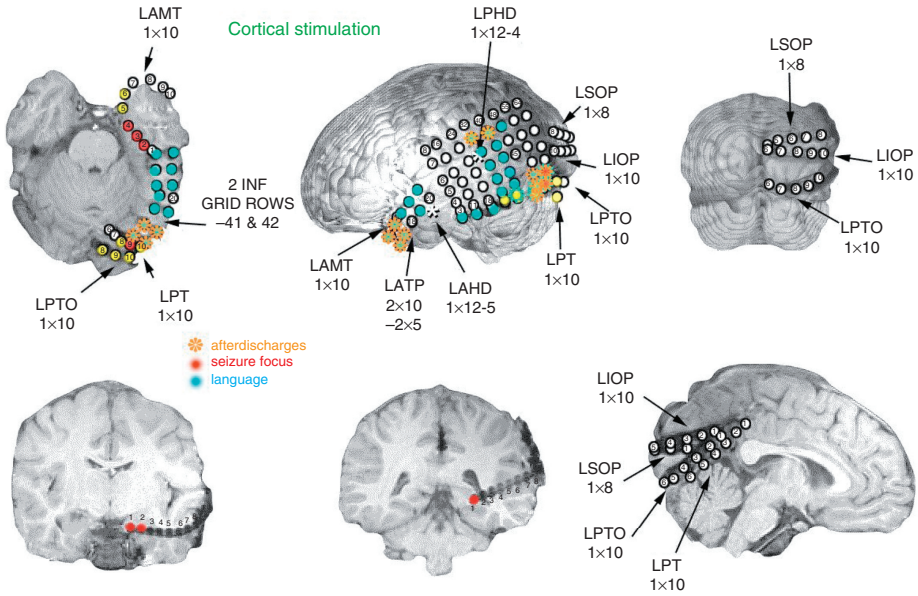


Plate 62.1 Cortical stimulation was undertaken after recording of seizures, including language mapping. The patient was brought to the operating room for resection of the left inferior occipital temporal region of epileptogenesis and multiple subpial transections of the left parieto-temporo-occipital area as it neared or overlaid language areas. A second-stage amygdalohippocampectomy was performed subsequently.

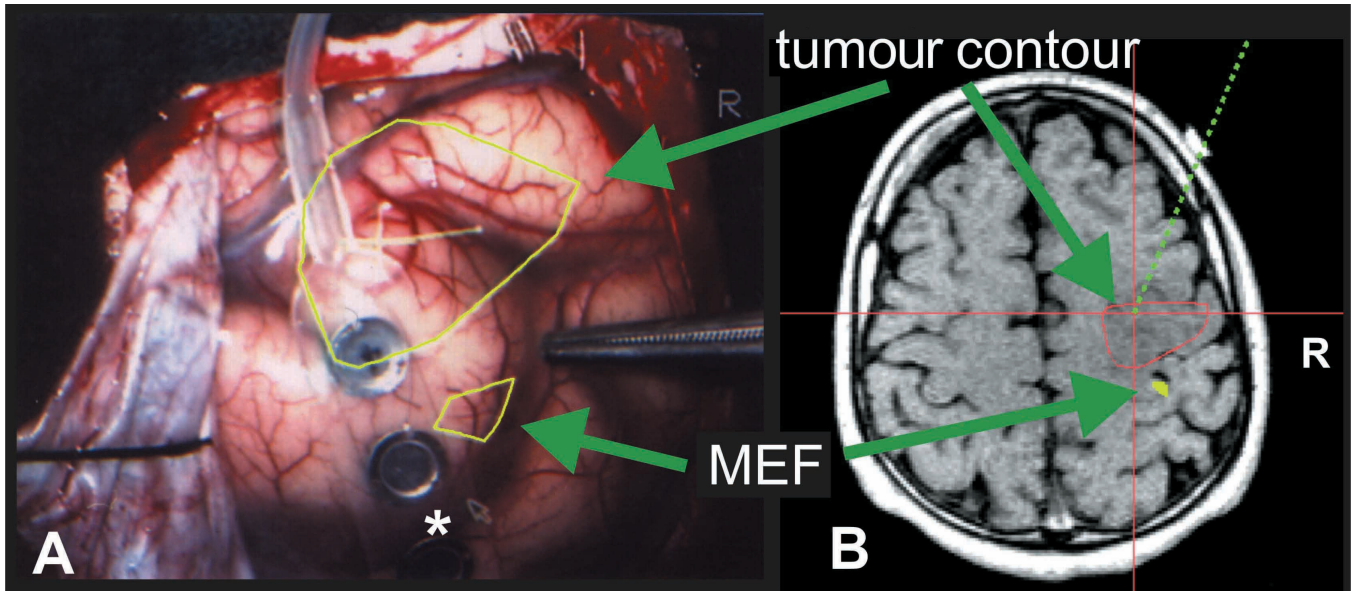


Plate 63.1 (a) Intraoperative view showing that in this patient the MEF dipole representing the motor cortex is displayed on the same gyrus as the tumour, which indicates that a resection is not possible. The white asterisk represents the SEF phase reversal and indicates the central sulcus. (b) Axial MRI showing the tumour countour and MEF dipole yellow triangle in the precentral gyrus, as displayed in the operating theatre for navigation purposes. Reproduced with kind permission from ref. 83.

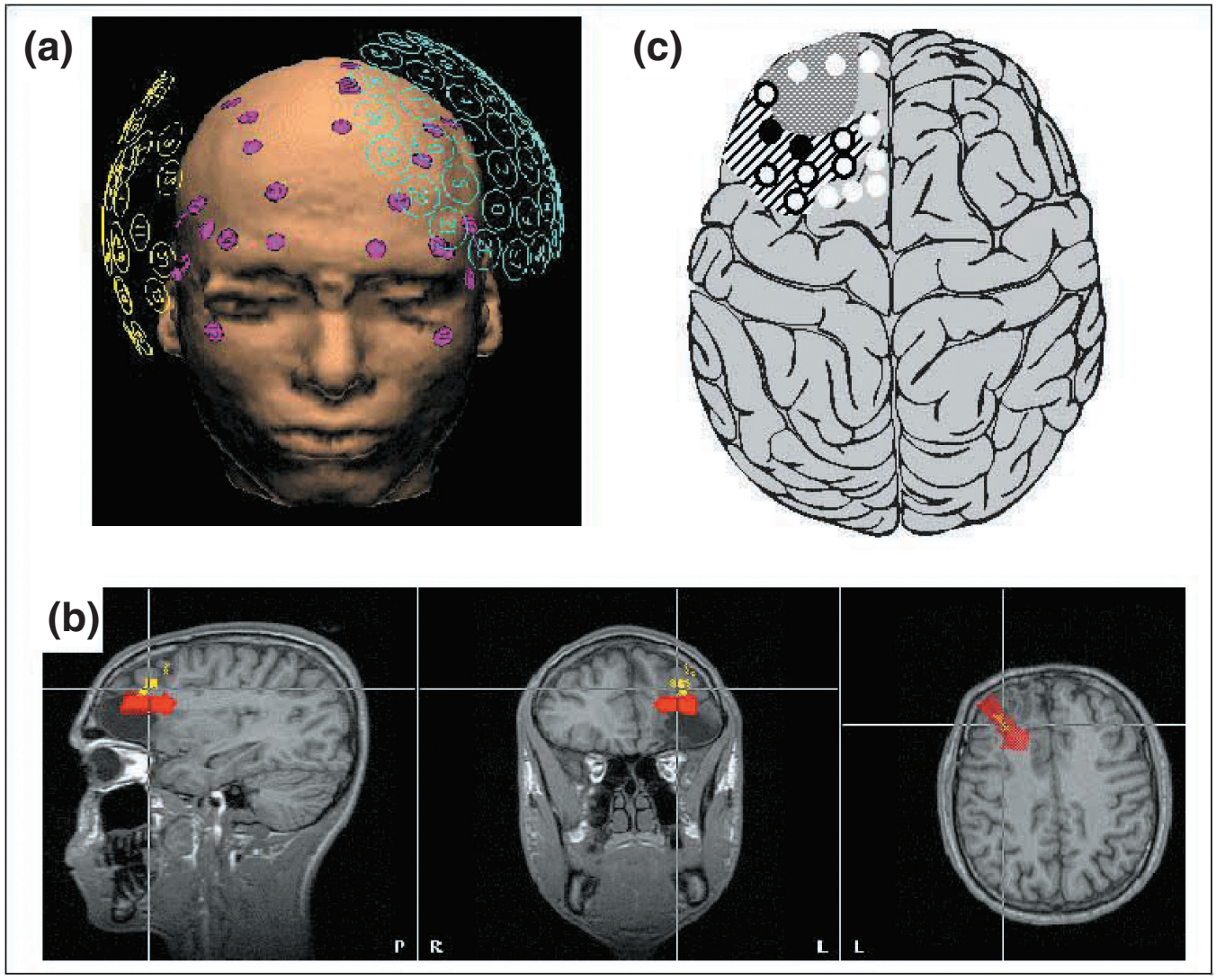


Plate 63.2 MEG and EEG localizations of interictal spikes in a patient with symptomatic frontal lobe epilepsy; with EEG spikes only identifiable after averaging according to MEG templates: (a) EEG electrode (magenta) and MEG sensor (cyan, yellow) locations. (b) Dipole sites, displayed in sagittal, coronal and axial MRI slices. Red: MEG results. Yellow: EEG results (showing higher variability). (c) Sketch of the intraoperative situation. Circles indicate ECoG contacts. Black: maximum spiking activity, in accordance with localization results in (b). White open: no spiking observed. Black-white: medium spiking activity. Shaded area: lesion. Hatched area: resection.

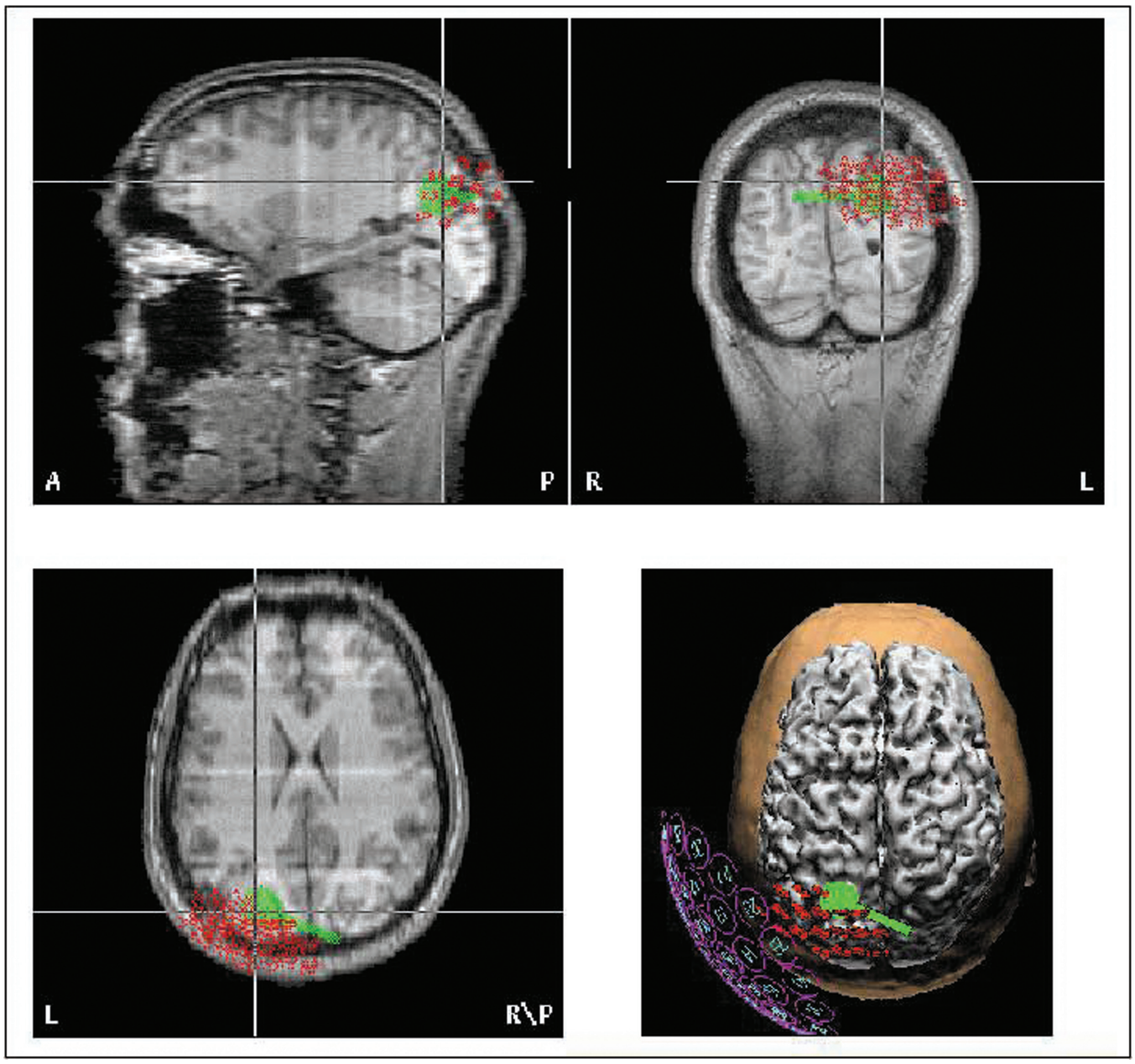


Plate 63.3 Ictal MSI localizations in a patient with symptomatic epilepsy of the left occipito-parietal region, displayed in sagittal, coronal and axial MRI slices (top and bottom left), and in a 3-D reconstruction of the cortex and skin compartments (bottom right). Red: area resulting from current density reconstruction. Green: dipole site. Numbers in magenta circles indicate MEG sensor positions.

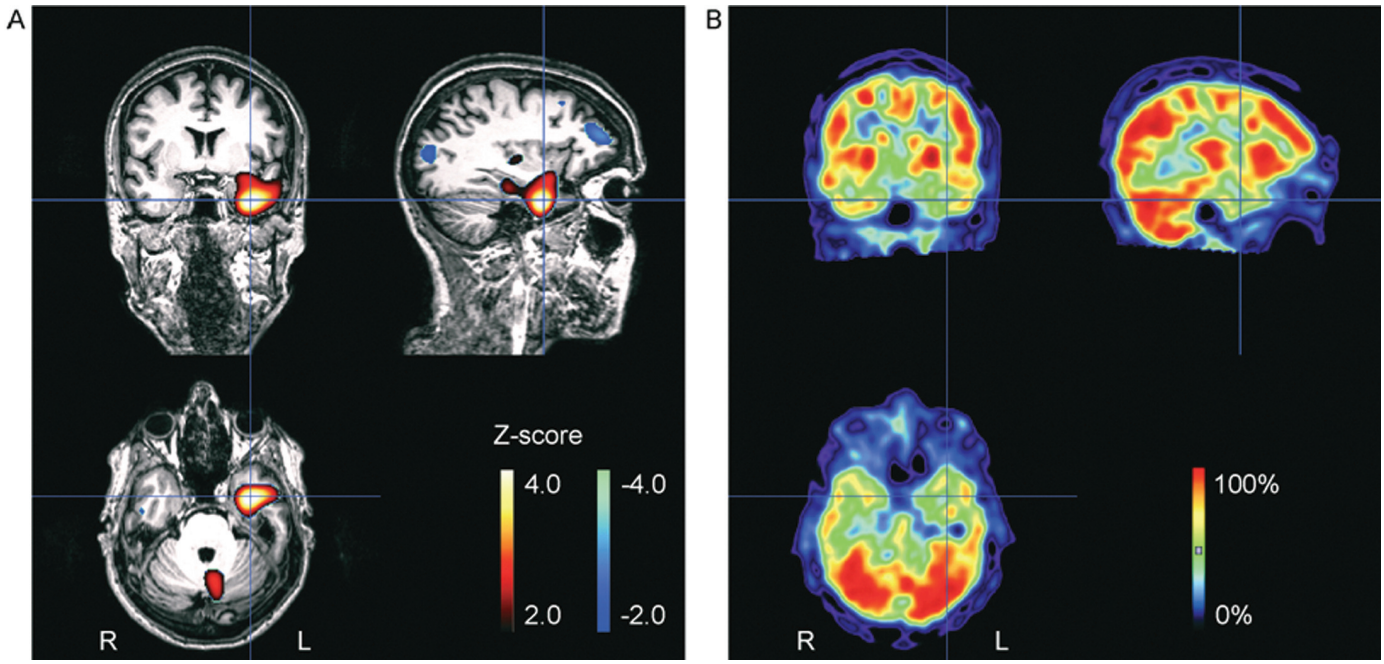


Plate 65.1 SISCOM (a) and FDG-PET (b) images of a 42-year-old patient with left TLE and normal MRI. SISCOM analysis showed a large cluster of ictal hyperperfusion located at the left temporal lobe (indicated by the blue cross). The ictal SPECT injection was given during a complex partial seizure that lasted 67 s, with initiation of the injection 35 s after seizure onset. FDG-PET showed a subtle hypometabolism in the same area. All images were co-registered. These functional imaging data were concordant with electroclinical and neuropsychological data and were considered an important argument to proceed to surgery. The patient underwent a neocortical temporal lobectomy including amygdala, but with sparing of the hippocampus and has remained seizure free. Neuropathological examination did not reveal an epileptic lesion. Reprinted from *Sem Nucl Med* (ref. 87), ©2008 with permission from Elsevier.

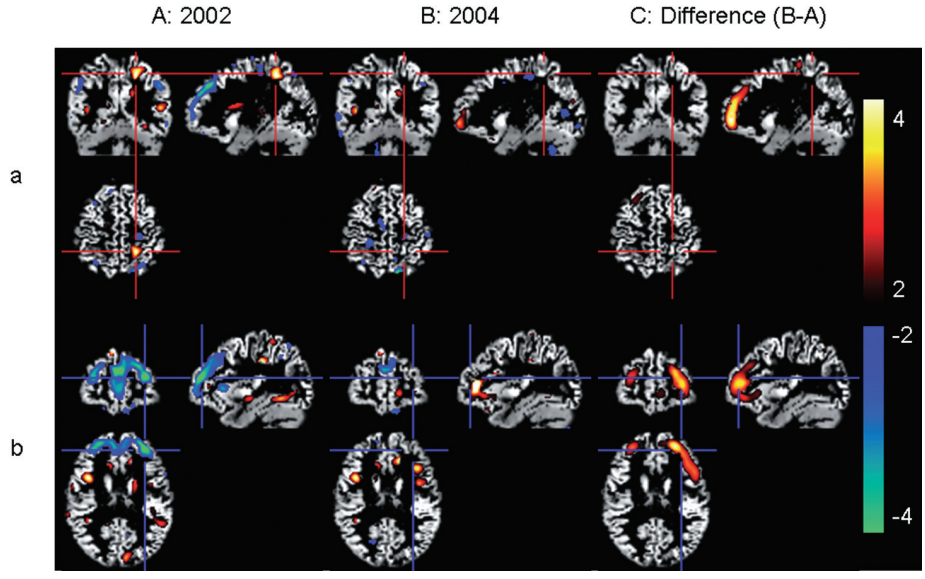
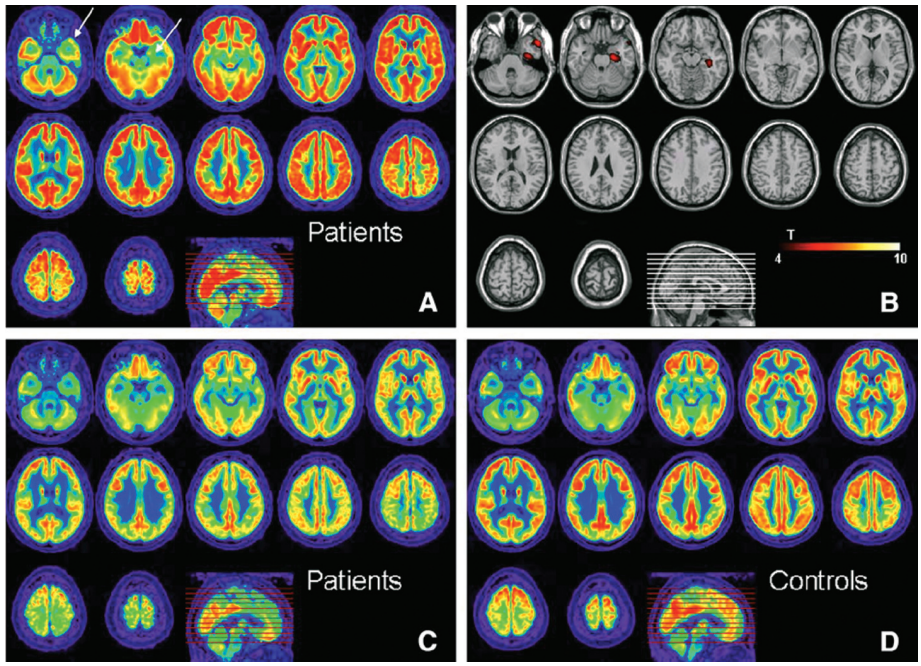
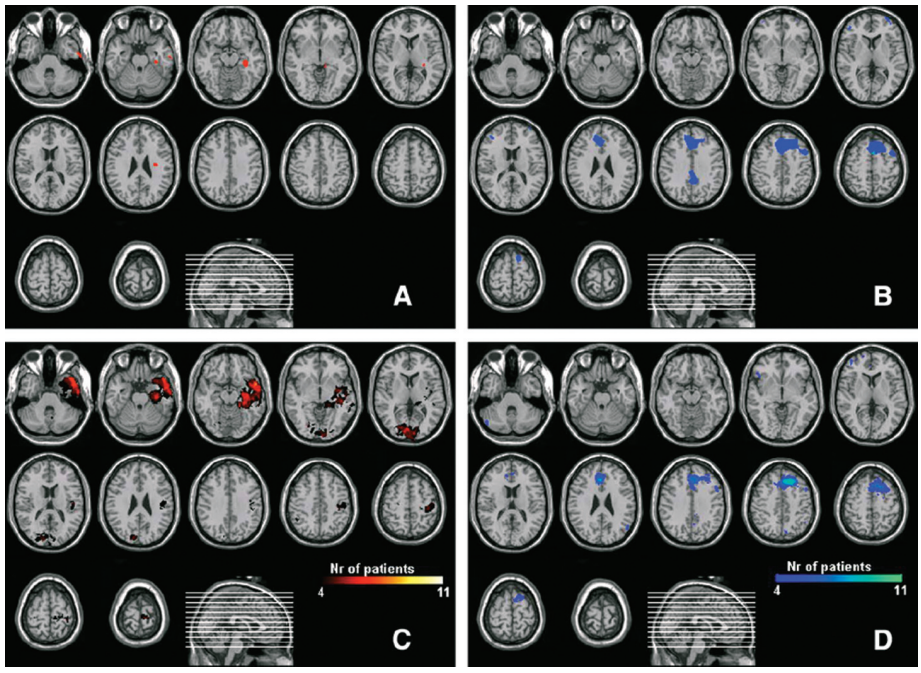


Plate 65.2 Ictal FDG-PET hyper- and hypometabolism during simple partial status epilepticus and recovery of metabolic abnormalities after seizure remission. The patient is a 21-year-old woman with a 3-month history of a simple partial status epilepticus of the left parietal lobe, characterized by continuous paraesthesiae in the right arm. Around 1 week before the ictal FDG-PET, she had a convulsive status epilepticus. The PET images were reconstructed using an anatomy-based reconstruction algorithm analysed semiquantitatively after normalization to white matter activity, and compared with a normal age- and gender-matched control group (for more details see refs 12, 14 and 25). Regions of significantly increased (>2SD, orange-red) and decreased (<2SD, blue-green) metabolism, compared with normal control subjects, are projected on a reconstructed PET image. The top row (a) shows the results in the left parietal region (red crosses) and the bottom row (b) in the left frontal region (blue crosses). FDG-PET during the simple partial SE (A, 12 April 2002) showed hypermetabolism in the left parietal region (a, part A), consistent with ictal activity, and large regions of hypometabolism affecting predominantly the frontal lobes (b, part A). The FDG-PET during remission of epilepsy (B, 2004) showed resolution of the left parietal hypermetabolism (a, part B) and frontal lobe hypometabolism (b, part B). The difference image between the two PET scans (a, part C and b, part C) showed the largest (>2 SD) increases in metabolism (orange-red) in the frontal lobes, left > right (b, part C), during remission of the epilepsy compared with the simple partial SE. This figure illustrates the dynamic, seizure-related character of the metabolic changes, and that ictal hypometabolism is mainly present in seizure propagation pathways, and does not define the ictal onset zone. At the time of scan A, she had severe cognitive deficits, which had normalized at the time of scan B. Reprinted from *Epilepsia* (ref. 45), ©2007 with permission from the International League Against Epilepsy, Blackwell Publishing.



(a)



(b)

Plate 65.3 (**a**) Frontal lobe hypometabolism in mesial TLE with HS. (a: part A) Mean image of the normalized FDG PET across a group of patients with TLE due to HS shows that the ipsilateral temporal lobe (white arrows) is more hypometabolic than the contralateral side, and appears to be the most hypometabolic region in the brain. (a: part B) SPM T-map (uncorrected *P*-value < 0.001) shown on the MRI of a single subject in MNI space confirms that a significant asymmetry in interhemispheric metabolism is only found in the temporal lobes. (a: parts C and D) Mean images of the normalized FDG-PET across patients with TLE (a: part C) and control subjects (a: part D), displayed using the same colour table, show a striking hypometabolism in the frontoparietal lobes in patients compared with control subjects. The hypometabolism in the epileptic temporal lobe, on the other hand, is less striking than the changes in the extratemporal regions. (b) Composite SPECT-PET Images. Top row: Images showing voxels in which a significant interictal hypometabolism was seen in combination with a significant ictal hyperperfusion (b: part A, voxels in red) or with a significant ictal hypoperfusion (b, voxels in blue). The results were obtained from a group analysis. Bottom row: Composite images showing the number of patients in a voxel in which hypometabolism (i.e. $z_{PET} < -1$) was seen in combination with ictal hyperperfusion ($z_{SPECT} > 1$) (b: part C) or with ictal hypoperfusion ($z_{SPECT} < -1$) (b: part D). The results were obtained from the individual analysis of each patient. The number of patients in each voxel was projected on the MRI of a single subject available in SPM2, and the right side of the image is ipsilateral to the seizure focus. The colour scales in (b: part C) and (b: part D) indicate the number of patients (maximum: 11). Reprinted from NeuroImage (ref. 25), ©2006 with permission from Elsevier.

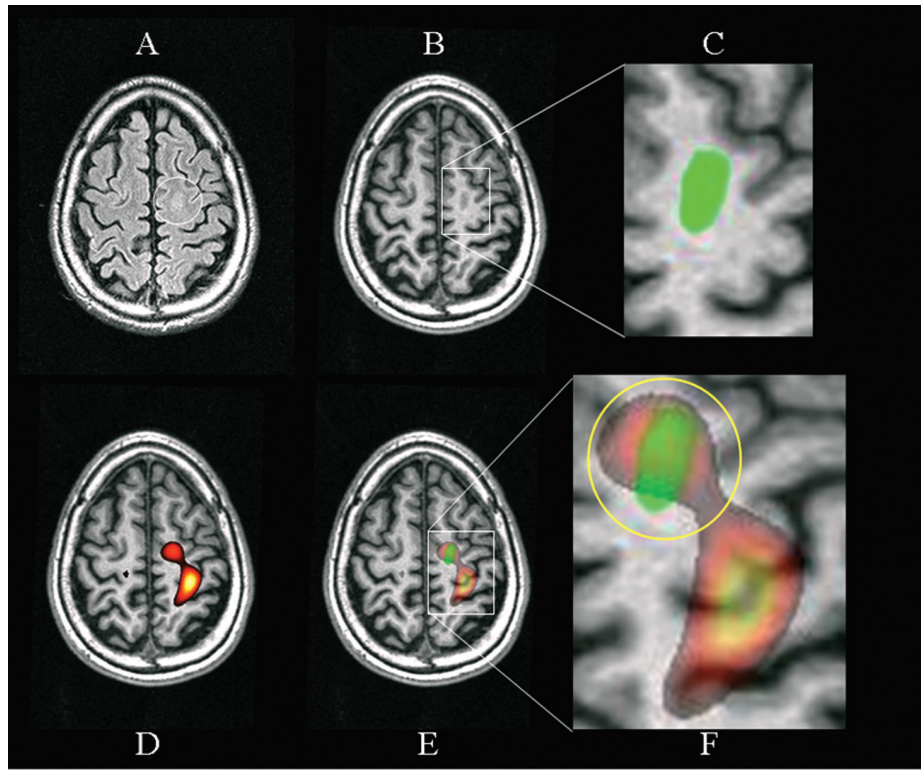


Plate 65.4 Ictal perfusion SPECT propagation pattern 2. A FLAIR image showed an increased signal in the left superior frontal gyrus (a, white circle), and on a T1-weighted image (b), there was blurring of the grey-white matter transition, consistent with an FDL. The FDL was manually outlined in green (c). The ictal perfusion SPECT injection was given during a complex partial seizure that lasted 70 s, with initiation of the injection 18 s after seizure onset. On a SISCOM (d), thresholded at $z = +2$, the cluster with the largest size had the configuration of an hourglass. Co-registration of the manual outline of the FDL and SISCOM (e) showed that the voxel with the lower local maximal *z*-score fell within the FDL, and that the highest *z*-score was at a distance of 28 mm from the FDL, measured from the margin of the manual outline of the FDL. Taking all the information of the presurgical evaluation into consideration, which was concordant, we considered the region containing the FDL and the part of the SPECT cluster with the lower local maximal *z*-score, up to the 'bottleneck of the hourglass' as the epileptogenic zone (f, yellow circle), and decided to operate the patient on the basis of these data. The patient has remained seizure free since the operation with a follow-up of more than 1 year. Reprinted from *Curr Opin Neurol* (ref. 88), ©2007 with permission from Lippincott Williams & Wilkins.

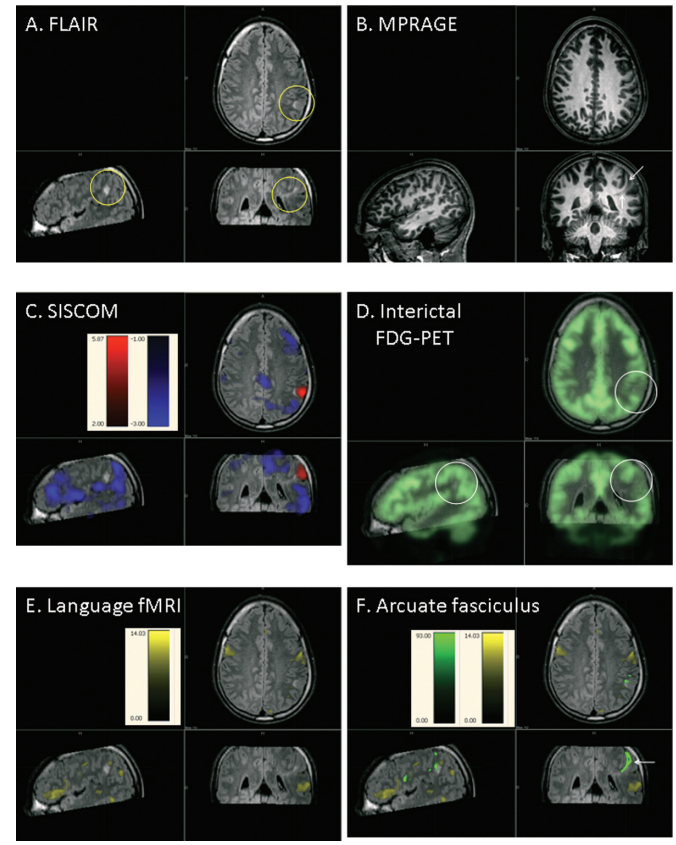


Plate 65.5 Multimodality imaging. The patient had refractory partial epilepsy due to a focal dysplastic lesion in the left supramarginal/angular gyrus, which was visible as a hyperintense lesion with transmantle sign on FLAIR (a, yellow circles) and as thickened cortex with blurred grey–white matter transition on a T1-weighted image (b, white arrows). Patient had an ictal SPECT with injection of the radioligand 5 s after the end of a complex partial seizure that lasted 16 s. The largest and most hyperintense SISCOM hyperperfusion cluster partially overlapped the focal dysplastic lesion (c, red area). Notice the large areas of hypoperfusion (c, SISCOM, blue areas) surrounding the ictal onset zone, which is not seen in *ictal* SISCOMs, which is consistent with the hypothesis of 'surround inhibition'. Interictal FDG-PET showed that the region of the focal dysplastic region was hypometabolic (d, white circles). Language fMRI (e) in this right-handed patient showed a bilateral language network with left-sided predominance. On the left side, Broca's (b) and Wernicke's (W) area were at a distance from the focal dysplastic lesion. Diffusion tensor tractography of the arcuate fasciculus showed that fibres connecting Broca's and the inferior parietal lobule crossed the focal dysplastic lesion (f, green tract, white arrow). Our surgical strategy would be to remove the focal dysplastic lesion and region of overlapping SISCOM hyperperfusion cluster. Although the lesion was outside the classical language areas, i.e. Broca's speech and Wernicke's comprehension centres, and the interconnecting arcuate tract, our imaging data suggested that the lesion was in the indirect pathway of perisylvian language networks [89]. Damage to this region could cause conduction aphasia, necessitating further functional studies preoperatively.

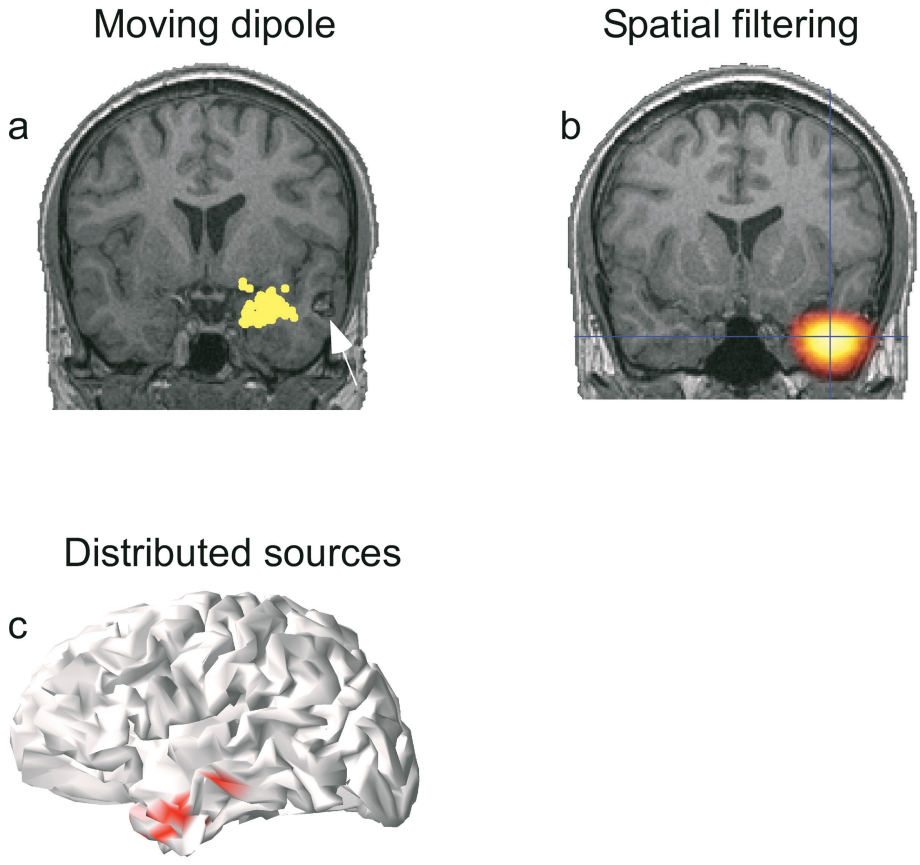
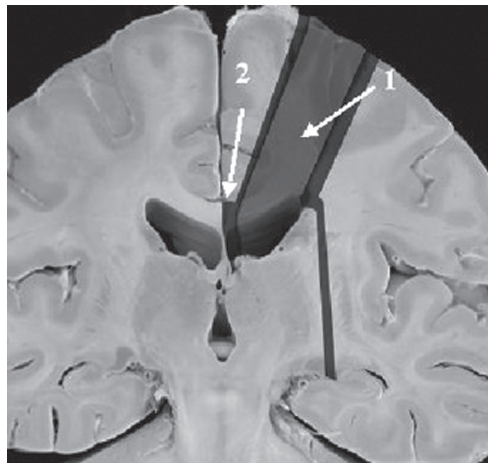
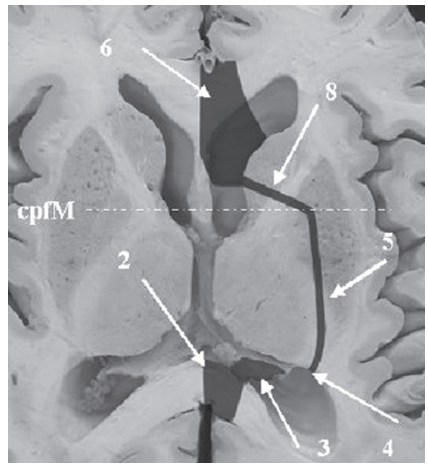


Plate 66.1 Approaches in modelling sources of interictal spikes. The figure shows results of source localization of epileptic spikes using different modelling approaches in the same patient suffering from partial epilepsy related to a left temporal cavernoma (white arrow). (a) Moving dipole: yellow dots represent estimated sources of individual spikes with goodness-of-fit >95%. Each individual source is punctual. (b) Spatial filtering: the pathological volume represents the estimated source extent of spikes. In this approach, the frequency content of the spikes is first estimated (here 65 Hz) and source localization procedures estimate the sources of the frequency content of epileptic spikes. (c) Distributed sources: the pathological volume has been determined with the weighted minimum–norm algorithm applied on averaged spikes. In this approach, dipolar sources are regularly placed along the surface of the cortical mantle obtained following segmentation of the MRI volume and the algorithm estimate the strength of currents underlying epileptic paroxysms for each source.



(a)



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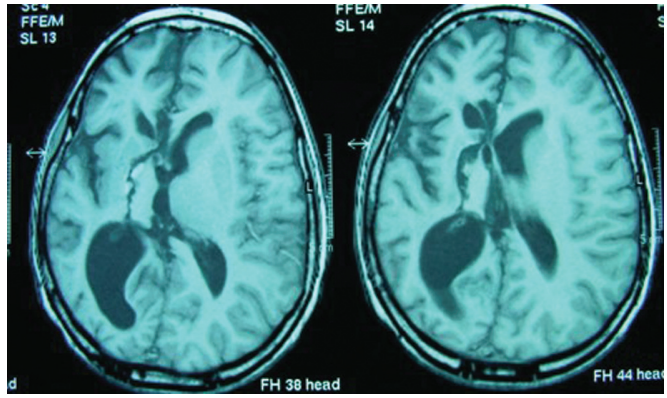
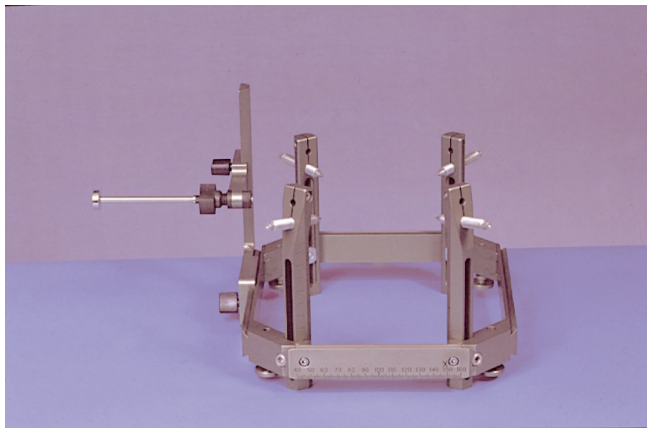


(c)

Plate 73.1 (a) Vertical parasagittal hemispherotomy. (a) Coronal plane demonstrating the cortical parasagittal window to the lateral ventricle (1), followed by the posterior callosotomy (2), which will be pursued towards the splenium. The vertical black bar towards the temporal horn represents the laterothalamic incision. (b) Following resection of the ipsilateral splenium (2), the floor of the ventricular trigone (3) will be sectioned, thus interrupting the foniceal fibres. The laterothalamic incision is then performed (4, 5). Following anterior completion of the callosotomy, the posterior part of the gyrus rectus is resected (6) and, from here, the dissection line is guided laterally across the frontal horn and the caudate nucleus (8), thus completing the disconnection of the entire hemisphere. (c) Postoperative axial MRI in a patient with Rasmussen's encephalitis, demonstrating the line of the laterothalamic disconnection. Figures reproduced with permission from Delalande O, Bulteau C, Dellatolas G *et al*. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. *Neurosurgery* 2007; **60**(ONS Suppl. 1): ONS1–ONS32.



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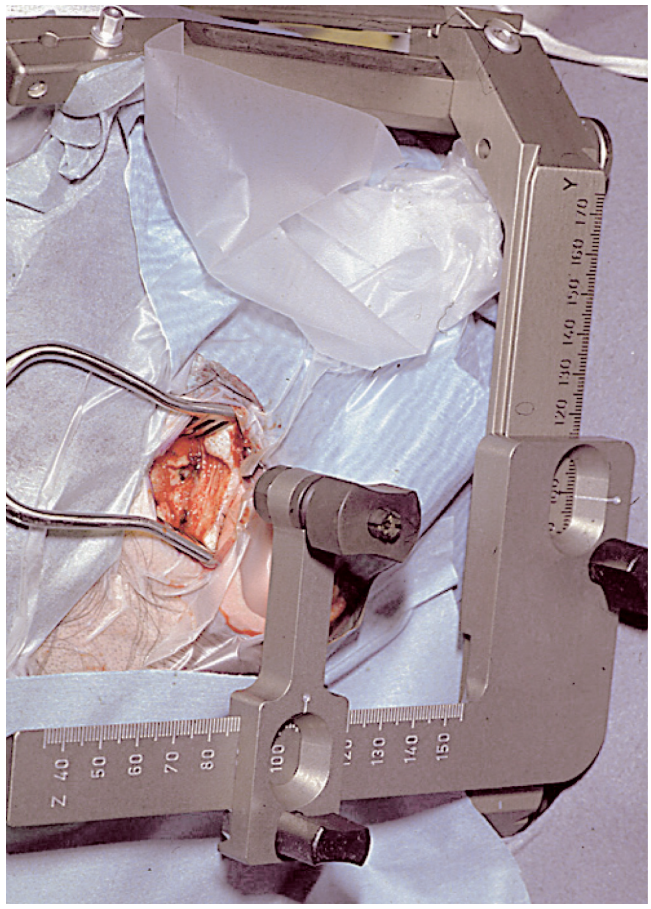

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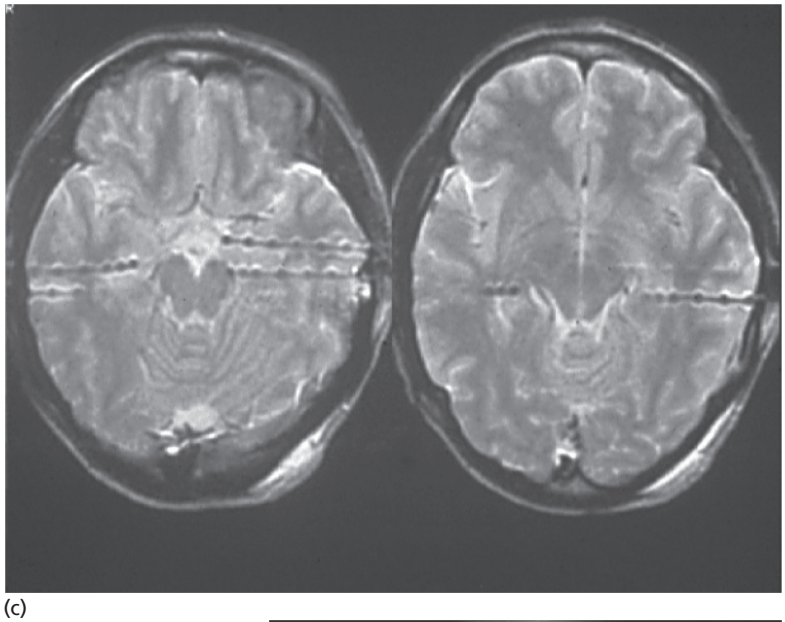

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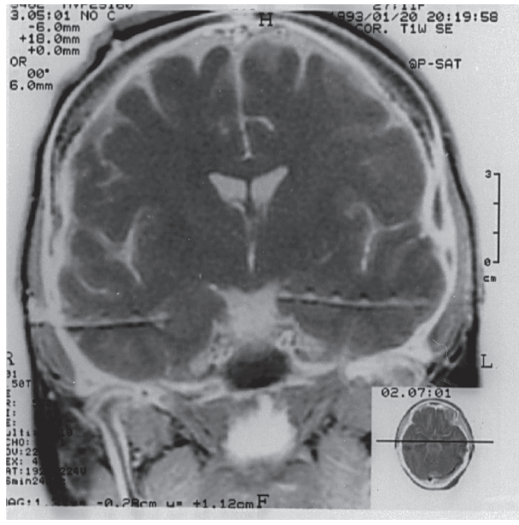

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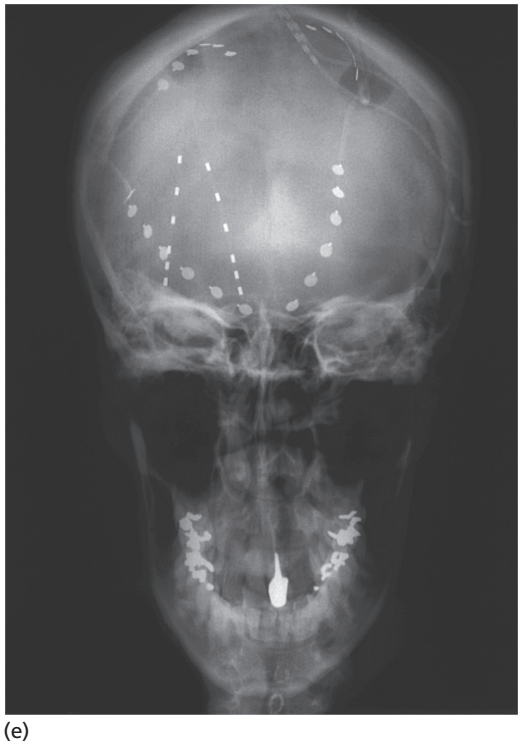
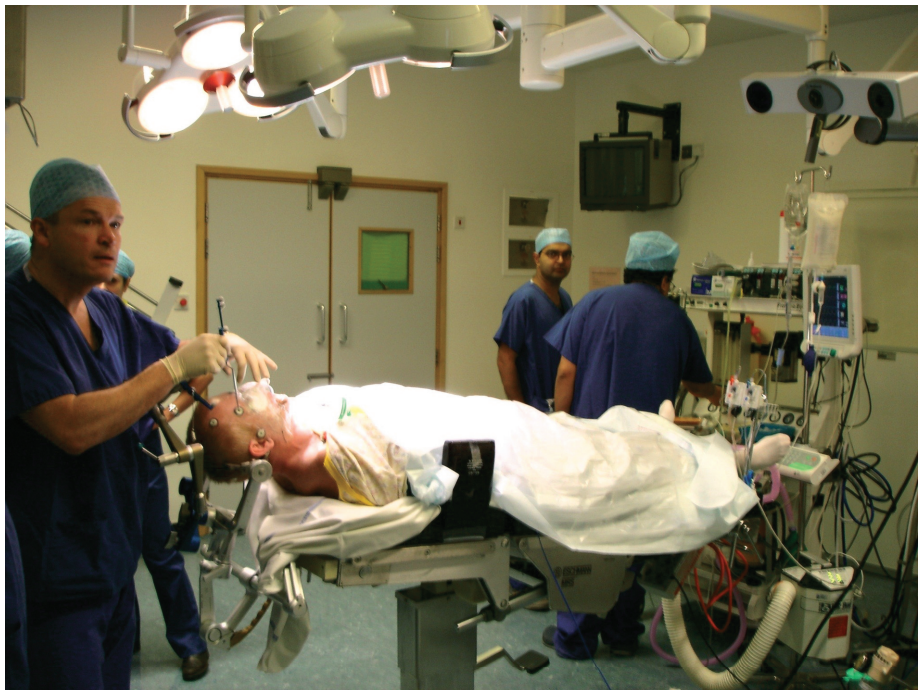
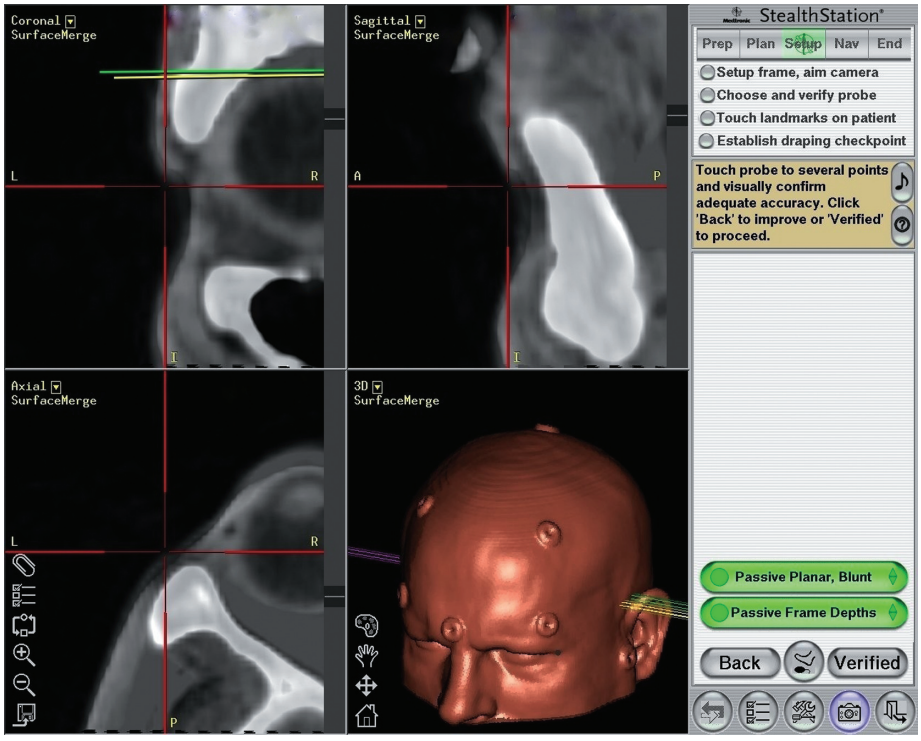


(e)

Plate 78.1 Following electrode placement confirmatatory radiological imaging is used to show the final position achieved, as it is critical to know precisely where the EEG recordings are emanating from in order to obtain an accurate three-dimensional picture of seizure activity. Usually, disposable multiple contact platinum electrodes are used. (a) The Lexell stereotactic frame. (b) The Lexell frame being used intraoperatively for the insertion of depth electrodes. (c,d) Axial and coronal MR showing depth electrodes bilaterally placed in the temporal lobes. (e) Anteroposterior radiograph of the skull, showing bilateral placement of subdural grid electrodes and right-sided frontal depth electgrodes.

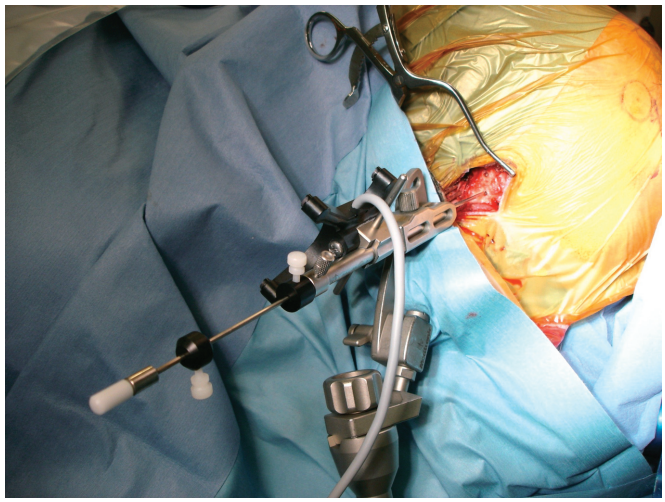


(a)



(b)

Plate 78.2 Modern frameless stereotaxy. The Medtronic StealthStation® neuronavigation system in use for placement of depth electrodes. (a) The patient's head must be fixed in Mayfield pins throughout the procedure. There must be unrestricted lines of sight between the exploratory probe and the camera receiver. (b) The fiducial points are carefully loaded into the computer so that image space can be accurately mapped to patient space. (c) The system is then ready for neuronavigation with a light-emitting diode probe. (d) The trajectory of the probe tip is demonstrated relative to multiplanar preoperative imaging enabling an accurate trajectory for insertion of the depth electrode.



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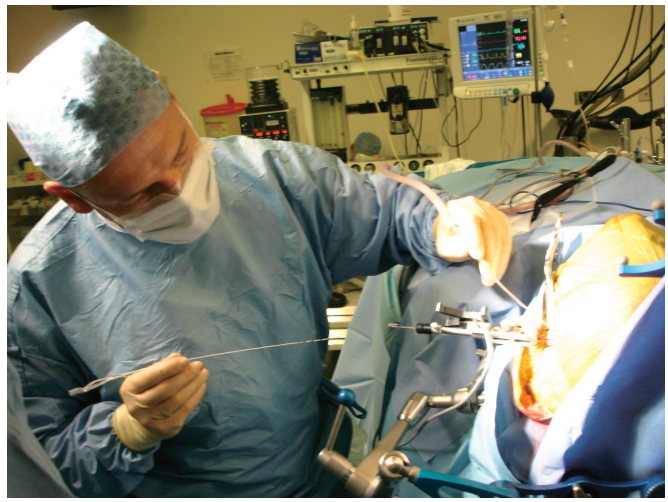
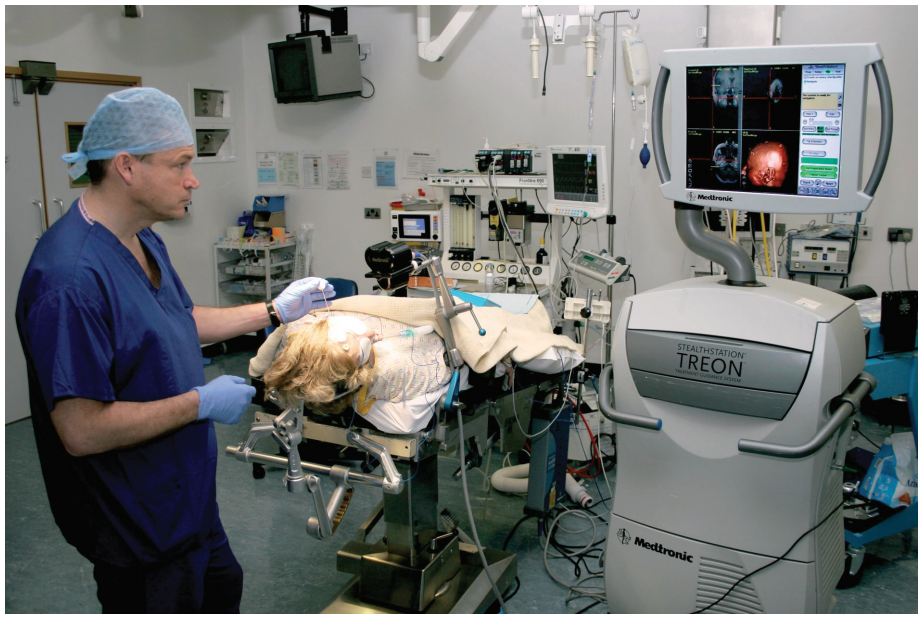
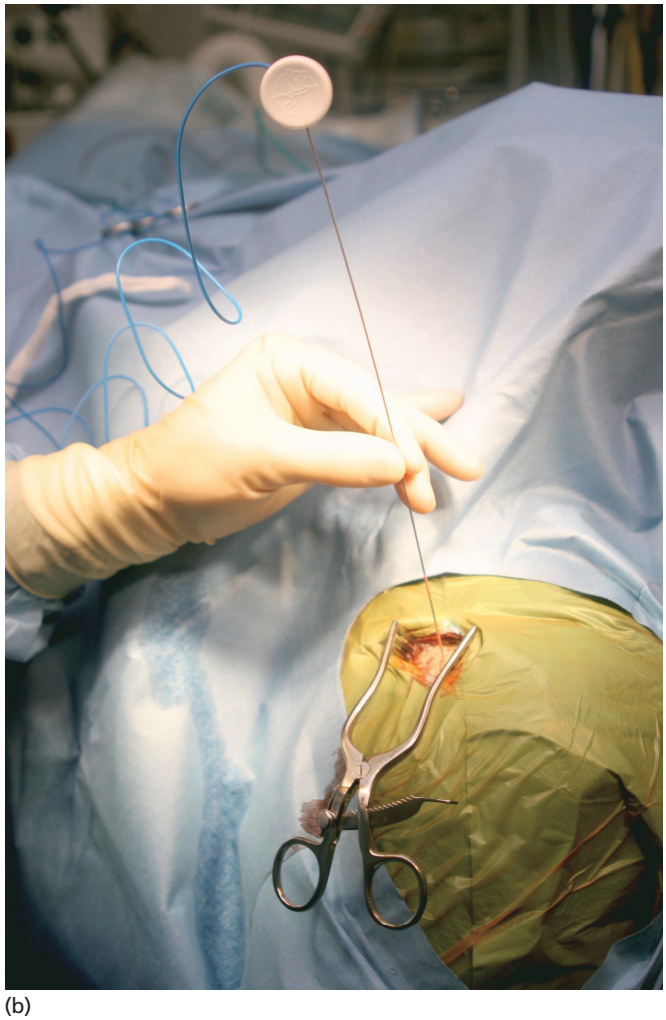


(d)

Plate 78.2 *Continued*



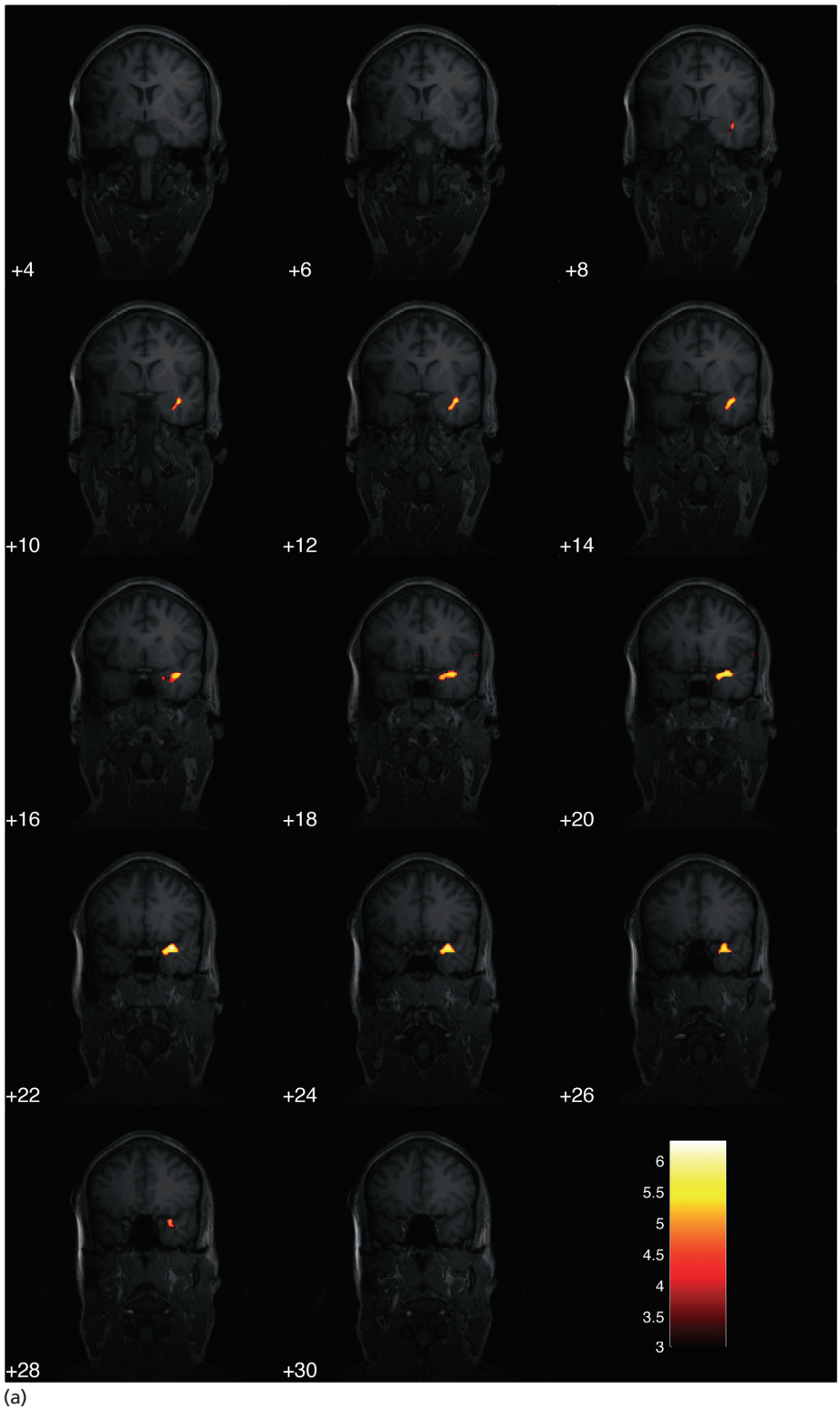
(a)



(b)

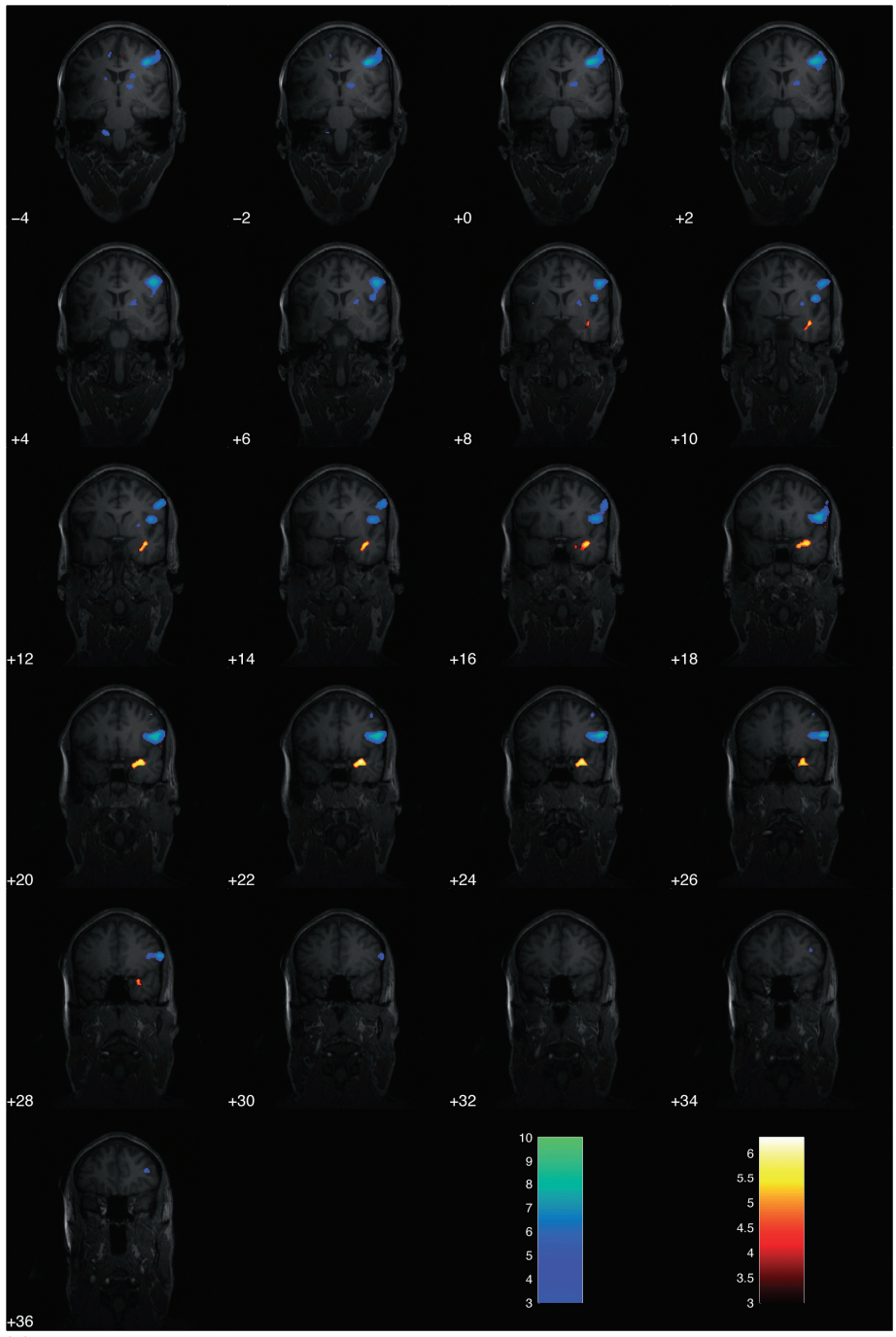
(c)

Plate 78.3 The Medtronic StealthStation® Axiem™ neuronavigation system in use for biopsy of a tumour. (a) The patient's head no longer needs to be fixed in Mayfield pins. An electromagnetic field is generated around the patient's target anatomy that can be tracked to triangulate the positioning of instruments and patient-tracking devices, so the system is no longer dependent on a camera's line of sight. The fiducial points are carefully loaded into the computer so that image space can be accurately mapped to patient space. (b) The system is then ready for neuronavigation with a flexible instrument tracked at the tip. (c) The trajectory of the probe tip is demonstrated relative to multiplanar preoperative imaging, enabling an accurate trajectory for insertion of the biopsy needle.



(a)

Plate 78.4 (a) Coronal EEG-correlated functional MRI, demonstrating interictal epileptiform discharges originating in the left temporal lobe. EEG-correlated functional MRI enables investigation of the haemodynamic correlates of interictal epileptiform discharges, thus enabling more precise localization of the epileptogenic focus. (b) Coronal EEG-correlated functional MRI in the same patient, demonstrating areas activated during verbal fluency testing. Using this technique to accurately define an area of brain function in relation to the epileptogenic focus can minimize surgical morbidity.



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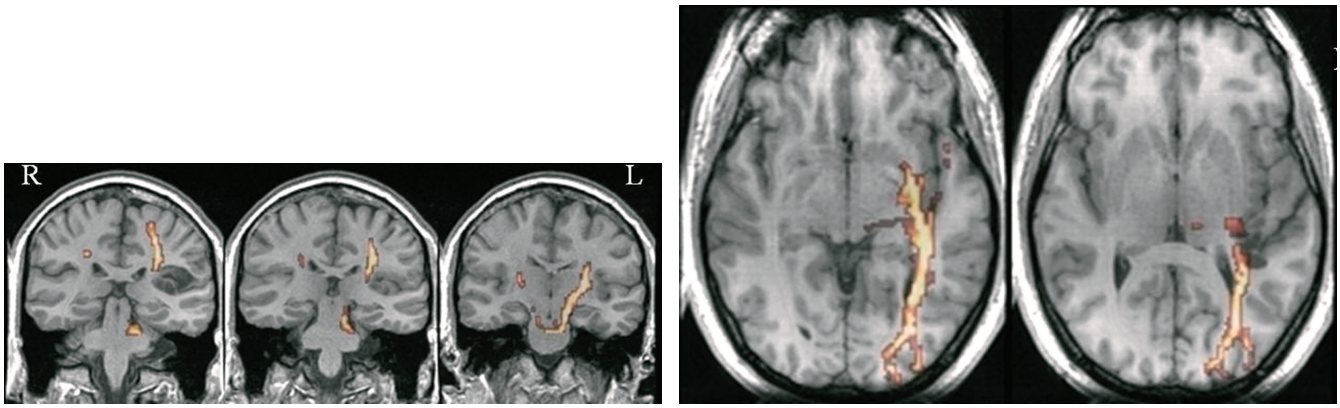

(a) (b)

Plate 78.5 (a) Coronal MRI with tractography, demonstrating the relationship of the corticospinal tract medial to the tumour. Knowledge of the relationship of the tumour to white matter tracts can minimize surgical morbidity. (b) Axial MRI with tractography in the same case, demonstrating the relationship of the optic tracts to the tumour.

1

Section 1
Introduction

The Treatment of Epilepsy, Third Edition Edited by S. Shorvon, E. Perucca and J. Engel
 ISBN: 978-1-405-18383-3

1 Definitions and Classification of Epilepsy

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More than a century and a half ago, Hughlings Jackson defined an epileptic seizure as the clinical phenomenon resulting from 'an occasional, sudden and excessive discharge of gray matter' [1], a definition that has stood the test of time. Over the years, the motor, sensory and autonomic phenomena that are produced by epileptic brain discharges have been identified and classified. Today, as in Jackson's time, seizures remain important signals to the possibility of underlying brain disorders that need to be identified and treated. Seizures are symptoms of abnormal brain function.

Epilepsy, like a seizure, is a symptom of abnormal brain function. Epilepsy is recurrent seizures that are not due to easily reversed, transient metabolic or toxic disorders. Seizures are fundamental elements of epilepsy. Although a causative brain disease can be identified in some cases, in the majority of cases no cause can be found and the best diagnosis possible is only descriptive. Of course, the goal in all cases is to identify the aetiology and pathoanatomical basis for the symptoms, but this is achieved in fewer than one-half of all cases. To summarize, there are two levels of descriptive diagnosis. The most elementary is according to the type of epileptic seizure. The more comprehensive system of descriptive diagnosis categorizes types of epilepsy or epileptic syndromes. The descriptive classifications of seizures and epilepsy are the subjects of this chapter.

Classification of seizure types

The currently used classification of seizures evolved from seminal work undertaken in the mid-1960s, which was published in 1969 [2] and 1970 [3], revised in 1981 [4] and updated in 2006 [5] (Table 1.1). The 1981 product was the result of combined videotaping and electroencephalogram (EEG) recordings of seizures that were reviewed and categorized in workshops convened between 1975 and 1979. Unlike previous schemes, the 1981 classification did not consider evidence of brain pathology, age and aetiology but instead restricted the basis for classification to clinical seizure types plus EEG data. The accepted seizure classification system has as its basis the current knowledge of anatomical substrates and pathophysiological mechanisms, and attempts to be a purely semiological classification system.

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Seizures are divided into two primary categories, based on whether the seizure arises in a restricted part of the brain in one hemisphere (focal seizures) or appears to involve both hemispheres from the onset (generalized seizures) [4]. A third category (unclassified seizures) is provided for cases that lack sufficient information for categorization.

Focal seizures

Historically, partial seizures have been subdivided into three groups – simple partial, complex partial or partial secondarily – generalized according to whether consciousness is impaired or the seizure evolves into a generalized convulsion as the epileptic brain discharge extends to involve both hemispheres. Partial seizures are classified as simple if consciousness is unimpaired during the episode. The label complex partial is applied if consciousness is impaired at any point during the ictus. Note that consciousness need only be impaired, not fully lost, to qualify the seizure as complex partial. Secondary generalization of the partial seizure typically overshadows the preceding partial seizure and, for this reason, many secondarily generalized seizures with partial onset go unappreciated by inexperienced observers only to be reclassified accurately after more details are elicited [6]. Hence, it is always important to ask the patient and witness(es) to describe in detail, step by step, the sequence of events that led to a convulsion.

Simple partial (or focal) seizures

The components of epileptic seizures can include any brain-modulated bodily function. Hence, seizures include any movement, sensation, perception or emotion of which humans are capable. However, the behavioural elements of seizures typically are situationally inappropriate, fragmentary manifestations of brain activity and thereby stand apart from smoothly integrated, situationally appropriate behaviours generated by normal brain functioning.

Movements or motor signs in partial seizures depend on the region of brain in which the epileptic discharge takes place. If the seizure is confined to a discrete area, isolated twitching or jerking occurs. If the discharge spreads to contiguous cortical areas, the movement often extends stepwise to involve adjacent functional groups. The progressive spread of an epileptic discharge through the motor strip results in an anatomically contiguous spread of the epileptic jerking called a Jacksonian march or Jacksonian seizure. Partial seizures that affect speech centres may lead to speech arrest. The phenomenon of ictal repetition of syllables or

Table 1.1 The International League Against Epilepsy (ILAE) classification of seizure type (2006 report of ILAE Classification core group).

Self-limited epileptic seizures
Generalized onset
- Seizures with tonic and/or clonic manifestations
  - Tonic–clonic seizures
  - Clonic seizures
  - Tonic seizures
- Absences
  - Typical absences
  - Atypical absences
  - Myoclonic absences
- Myoclonic seizure types
  - Myoclonic seizures
  - Myoclonic astatic seizures
  - Eyelid myoclonia
- Epileptic spasms
- Atonic seizures

Focal onset (partial)
- Local
  - Neocortical
    - Without local spread
      - Focal clonic seizures
      - Focal myoclonic seizures
      - Inhibitory motor seizures
      - Focal sensory seizures with elementary symptoms
      - Aphasic seizures
    - With local spread
      - Jacksonian march seizures
      - Focal (asymmetrical) tonic seizures
      - Focal sensory seizures with experiential symptoms
  - Hippocampal and parahippocampal
    - With ipsilateral propagation to
      - Neocortical areas (includes hemiclonic seizures)
      - Limbic areas (includes gelastic seizures)
    - With contralateral spread to
      - Neocortical areas (hyperkinetic seizures)
      - Limbic areas [dyscognitive seizures with or without automatisms (psychomotor)]
- Secondarily generalized
  - Tonic–clonic seizures
  - Absence seizures
  - Epileptic spasms (unverified)

Neonatal seizures

Status epilepticus
Epilepsia partialis continua (EPC)
- As occurs with Rasmussen's syndrome
- As occurs with focal lesions
- As a component of inborn errors of metabolism

Supplementary motor area (SMA) status epilepticus
Aura continua
Dyscognitive focal (psychomotor, complex partial) status epilepticus
- Mesial temporal
- Neocortical

Tonic–clonic status epilepticus
Absence status epilepticus
- Typical and atypical absence status epilepticus
- Myoclonic absence status epilepticus

Myoclonic status epilepticus
Tonic status epilepticus
Subtle status epilepticus

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phrases is called epileptic pallilalia. Continuous partial seizures, often lasting days or longer, are called epilepsia partialis continua.

Transient localized paralysis, lasting between minutes and hours following a partial or secondary generalized motor seizure, is called a Todd's paralysis. In some cases, focal postictal paralysis may be the only clue indicating that a generalized seizure had a partial onset.

Sensory symptoms that are produced by seizures also reflect the normal function of the brain region where the discharge is occurring. Frequently felt sensations include pins-and-needles and numbness. Sensory seizures that originate in visual cortex or auditory cortex produce visual and auditory hallucinations, respectively. As emphasized in the 1981 classification [4], epileptic hallucinations vary in sophistication from ill-formed patterns of light and sound to well-structured images and recognizable sounds such as music [4]. Ictal olfactory hallucinations tend to be vague but are generally disagreeable. Hallucinated tastes are frequently metallic. Vertiginous symptoms, such as hallucinated rotation or spinning, are relatively common. Unlike vertigo of vestibular origin, epileptic vertigo is usually not associated with nausea or severe anxiety and is rarely incapacitating.

When simple focal sensory seizures precede complex partial or secondarily generalized seizures, the premonitory experience is called an 'aura'. Attributed to Galen, the term 'aura' was derived from the Greek word *αερ* or air, meaning breeze, as it was used by a 13-year-old boy who described a sensation that began on his lower leg and 'climbed upwards in a straight line' [7]. Subsequently, the term 'aura' has been applied generally to include any premonitory ictal sensation.

Psychic symptoms

Psychic symptoms are among the most intriguing consequences of partial seizures. These result from discharges that interrupt higher cortical processes and are often associated with impaired consciousness and thereby become components of complex partial seizures.

The most common psychic symptoms are affective, especially the feeling of fear, or in the extreme, terror. These experiences are frequently accompanied by autonomic manifestations including mydriasis, change in skin colour, piloerection and other signs. When epileptic fear or anxiety occurs, the affected person may run to escape or to find a caretaker, seeking assistance. Children who experience ictal fear go to a parent and display fearful facial expressions.

Other affective symptoms include anger, rage, extreme pleasure, sexual sensations and, rarely, ecstasy. These experiences are typically brief and paroxysmal, beginning without warning or provocation, and ceasing abruptly as if an electrical switch were turned on and off. The time-course of the emotion is substantially shorter than normal. Furthermore, seizure-generated affect is usually inappropriate to the social context of the moment. Seizure-induced laughter characteristically sounds automatic, mirthless, hollow or vacuous and is not socially infectious like normal mirthful laughter. Seizures manifest by laughter are known as gelastic seizures.

Ecstatic seizures, also known as 'Dostoevsky seizures', are so rare that it is debated as to whether they truly occur [8]. Described

by the great author Fyodor Dostoevsky [9,10], these are brief moments of 'a contentedness which is unthinkable under normal conditions, and unimaginable for those who have not experienced it'. Dostoevsky went on to write: 'At such times I am in perfect harmony with myself and with the entire universe. Perception is so clear and so agreeable that one would give ten years of his life, and perhaps all of it for a few seconds of such bliss' [8].

Memory distortions are also reported frequently by people who experience complex partial seizures. Representing heightened perceptions of familiarity, déjà vu and déjà entendu refer to the intuition that an experience was previously seen or heard, respectively. Jamais vu and jamais entendu indicate the opposite: the experience is unfamiliar and was never before seen or heard. Panoramic vision is a rapid remembrance of previous life experiences.

Dysphasic psychic epileptic symptoms involve speech. Speech disturbances can occur as either an active part of the seizure (as when words or phrases are repeated) or postictally as transient neurological deficits due to cortical neuronal exhaustion. The latter produce receptive and expressive aphasias of the types seen in cortical deficits of other causes.

Cognitive psychic symptoms include dreamy states, distorted perception of time and reality as well as detachment or depersonalization in which the person feels as if he is outside his body.

Illusions are distorted perceptions. The visual illusions of an object being too large or too small are called macropsia and micropsia, respectively. Analogous distortions affect hearing, resulting in macro- and microacusia. Illusions can affect any simple or complex sensory modality. Examples include monocular diplopia and altered appreciation of limb size and weight.

Complex partial seizures

The *sine qua non* of complex partial seizures is impairment of consciousness. Premonitory sensory or psychic auras (simple partial seizures) frequently forewarn and lead into the complex partial episode. The nature of the sensory experience provides important clues about the origin of the seizure. However, many complex partial seizures begin with sudden impairment of consciousness.

Automatisms – repetitive, patterned, semipurposeful spontaneous movements – are a common feature of complex partial seizures. Gastaut described automatisms as 'more or less coordinated adapted (eupractic or dyspractic) involuntary motor activity occurring during the state of clouding of consciousness either in the course of or after an epileptic seizure, and usually followed by amnesia for the event' [5]. A pathophysiological explanation of automatisms is that these occur when bilateral cortical dysfunction lasts long enough to release the expression of patterned movements that are represented at lower brain levels but which are normally held in check by cortical inhibition [11,12]. As automatisms result from bilateral cortical dysfunction, consciousness is always impaired.

Automatisms are either perseverated continuations of previous movements or are novel behaviours. Common automatisms include chewing or swallowing movements categorized as 'eating'; expressions of emotion (usually fear) categorized as 'mimicry'; picking at or fumbling with garments (gestural automatisms); walking, often in circles (cursive seizures), categorized as 'ambulatory'; and, finally, verbal or repeated items of speech (also called epileptic pallilalia) [5].

Generalized seizures

Generalized seizures are produced by epileptic discharges that affect both hemispheres simultaneously. When this occurs, consciousness is usually lost or impaired.

Absence seizures

In absence seizures, consciousness is lost and regained in an abrupt off–on pattern. Behaviour or movement that is occurring at the onset may be perseverative but usually ceases instantly as the person begins to stare. During the staring, the eyes may gaze straight ahead or deviate upwards while the eyelids twitch faintly and rhythmically. Rarely lasting more than 30 s, absence seizures are usually quite brief, often less than 5 s. Absence seizures need to be differentiated from normal daydreaming and from complex partial seizures. The latter typically have a longer duration and last more than 60 s in untreated cases. In daydreaming, consciousness is intact, although responses to questions or commands may be delayed or slow. In absence and complex partial seizures, consciousness is impaired.

A good way to assess clinically whether consciousness is impaired is to present the person with several words and then ask him or her to repeat what was just said. For example, say to the person, 'Ball, yellow, girl' followed by 'What did I say?' Even young children usually respond correctly to this type of elementary request if consciousness is unimpaired. Repeatedly asking 'Are you alright?' usually does not help to determine whether consciousness was altered during brief staring episodes because if the questioning is repeated enough times, eventually the episode ends and the person answers appropriately. If a verbal response is not promptly forthcoming, gently touching the person can help further evaluate whether consciousness is impaired. When staring due to daydreaming cannot be differentiated from epileptic staring on clinical grounds, video EEG recordings of the episodes are usually diagnostic [13,14].

Atypical absence seizures

Although no single feature differentiates typical from atypical absence, atypical absence seizures are more likely to be associated with the following features: longer duration, decreased postural tone and tonic activity. Atypical absence seizures occur in patients with interictal abnormalities on EEG, multiple seizure types and mental retardation. Although the 1981 classification noted that the onset and cessation of atypical absence were not as abrupt as in the case of typical absence, subsequent investigation found that both types begin and end suddenly. However, postural changes and other features of atypical episodes tend to evolve gradually [2,14,15].

Myoclonic seizures

Myoclonus is a sudden brief involuntary movement (a jerk) that can originate from many regions and levels of the central nervous system [16]. Myoclonic seizures are myoclonic jerks that result from epileptic discharges in the brain. In the 1981 classification, myoclonic jerks were defined as 'sudden, brief, shock-like contractions.' As pointed out by Dreifuss [17], myoclonic seizures

occur in many different epileptic syndromes, which include benign and severe myoclonic seizures of infancy, symptomatic epilepsies due to systemic storage diseases or defects in energy metabolism. On the other hand, non-epileptic myoclonus occurs in spinal disease, cerebellar degeneration, uraemic encephalopathy, subcortical (brainstem) myoclonus and other syndromes. Occurring singly or repeated serially, myoclonic seizures may be generalized or limited to part of the body or a single muscle. Generalized myoclonic seizures that affect the body have been called massive epileptic myoclonus, a term that was introduced in the 1981 classification. Myoclonus epilepsy refers to several progressive disorders in which either epileptic or non-epileptic myoclonus is a prominent feature.

In practice, the terms myoclonic jerks, myoclonus, myoclonic epilepsy and myoclonus epilepsy are confusing because various authorities apply the terms for different purposes. The term myoclonic epilepsy has been used by some authors to describe a particular type of epilepsy and by others to define a group of several epilepsies in which patients have myoclonic seizures plus other features. This ambiguous terminology led Jeavons to comment in 1977 [18] that application of the term 'myoclonic' had become so confusing that he recommended defining the term whenever it was applied to seizures or epilepsy.

In some cases, the epileptic origin of the muscular jerking cannot be discerned on routine EEG but requires event-locked (also called jerk-locked) averaging of cortical potentials for the epileptic discharge to be visualized [19,20].

Clonic seizures

Clonic seizures are those characterized by repetitive, rhythmic jerking. In isolation, a single clonic movement has a rapid phase of contraction followed by a slower relaxation. In clonic seizures this results in an alternating pattern of jerk–relax, jerk–relax, etc. Note, however, that some generalized seizures evolve with the sequence of clonic–tonic–clonic phases.

Tonic seizures

Tonic seizures involve rigid, violent muscular spasms with posturing axial and limb musculature, which typically last 30 s or less with mydriasis plus eye deviation upwards or to the side. Tonic seizures end abruptly with variable to no postictal symptoms. During the seizure, the face is often distorted by the contraction and respiration is disrupted, often leading to cyanosis. Other variable features include slowly progressive alterations of tone, and versive movements with rotation, twisting or turning. As pointed out by Dreifuss [17], these need to be differentiated from non-epileptic dystonia. Isolated tonic seizures seem to be most common during sleep and may go unrecognized.

Tonic–clonic seizures

Tonic–clonic seizure is the term used for a generalized convulsion and was previously referred to as a grand mal seizure. Readily recognized by lay persons as a seizure or fit, it is characterized by a sudden fall and dramatic, violent and involuntary jerking and muscular spasm of the limbs and body. The episode begins suddenly with the simultaneous loss of consciousness and contraction of body musculature; this is the tonic phase during which the person becomes rigid and falls, often traumatizing the head or extensor surfaces of the body (Table 1.2). The tonic contraction first involves flexion and then extension of the axial muscles [21]. Contractions of axial muscles can be sufficiently forceful to cause compression fractures of the vertebrae [22]. Contraction of respiratory musculature leads to forced exhalation and vocalization in the form of a cry or moan. The eyes deviate upwards and pupils dilate. Incontinence can occur during the tonic phase or later when postictal exhaustion leads to relaxation of sphincters. During the tonic phase the individual may bite his tongue or cheek and respiration is disrupted, leading to cyanosis. During the tonic phase the EEG most often is characterized by high-frequency spike activity.

Table 1.2 Behavioural stages of generalized convulsive seizures.

Prodrome
Aura
Tonic phase
Clonic phase
Postictal unconsciousness and hypotonia
Postictal neurological deficit (Todd's paralysis)
Sleepiness
Return to normal functioning

During the maximal tonic contraction of body and limb muscles, the initial rigidity gradually evolves into irregular tremulous shaking, similar to that seen in supramaximal muscular exertion. This in turn evolves into generalized jerking – the clonic phase. In the clonic phase, generalized flexor spasms alternate with relaxation, causing irregular respiration, sometimes with grunting. Salivation is profuse and, when combined with lack of swallowing and an irregular respiratory pattern, leads to frothing at the mouth.

The oscillatory contractions during the clonic phase gradually slow and stop marking the end of the convulsion and the beginning of the postictal period. Although convulsions are frightening and seem long-lasting, most end within 60 s. Those seizures that do last longer than 60 s are statistically uncommon [23].

The postictal phase is characterized by diffuse hypotonia, slow, deep respirations and unresponsiveness. Over time, consciousness slowly returns but is clouded at first as awareness emerges from unconsciousness into partial comprehension with confusion. If the person is restrained or handled forcefully, he may resist combatively. The subsequent recovery over minutes to hours is marked by sleepiness, variable headache and complaints of musculoskeletal soreness upon awakening. Persistent back pain may indicate that a vertebral compression fracture occurred during the seizure.

Atonic seizures

Atonic seizures are those in which there is a sudden reduction or loss of postural tone and in which posture is affected to varying degrees. When the seizure is extensive, postural control is lost and the person drops or slumps to the ground, producing so-called drop attacks or astatic seizures. The latter term, 'astatic seizures', was not part of the 1981 classification but has become widely used since then. In part, this has occurred because most drop attacks are not due to atonic seizures, per se, but rather represent massive myoclonic seizures or combinations of atonic and myoclonic seizures that forcefully thrust down the person. Drop attacks or astatic seizures often result in injury to teeth plus lac-

erations and contusions of the head and face. Some atonic seizures alter tone in a restricted part of the body, causing head nods, head drops or lapses of limb posture. If consciousness is lost in atonic or in astatic seizures, the lapse is quite brief. The difference between partial or brief atonic seizures and so-called epileptic negative myoclonus is unclear [16,24]. As emphasized in the 1981 classification [4], other non-epileptic disorders can cause drops or lapse of posture. Other causes include cataplexy and brainstem ischaemic attacks.

Seizures not classified by the 1981 classification

Epileptic prodrome is the term applied to disturbances in mood and affect that precede seizures by hours or days. More often noted by companions or family members than by the person who has epilepsy, the behavioural characteristics, such as irritability and meanness, cause the observers to look forward to the seizure, after which the person's affect and mood normalize [25].

Classification of epilepsies and epileptic syndromes

The epilepsies, also known as epileptic syndromes, are characterized by other features in addition to seizure type. From the Greek *syn* + *dramein* (meaning to run with), the word syndrome indicates a group of signs and symptoms that occur together. Thus, epileptic syndromes are constellations of epileptic seizures plus concurrent or serially linked symptoms and signs. Seizures are the seminal elements that constitute an epilepsy, but other features largely differentiate the overall disorder or type of epilepsy (Table 1.3). As Professor Fritz E. Dreifuss was fond of saying, 'seizures are to epilepsy as a cough is to pneumonia'.

Complexity and utility of epilepsy syndrome classification

The current classification of epilepsies is empirical. It is the product of expert epileptologists who spent many hours viewing video recordings of seizures, discussing their observations and deliberating about whether clinically similar groups of patients represented discrete clinical entities. At the time the syndromes were being codified, knowledge regarding the genetic neurobiological basis of epilepsy was rudimentary.

Individual metabolic and genetic causes of seizures can produce many different patterns of epilepsy. For example, the epileptogenicity of pyridoxine deficiency was recognized in the 1950s, but it took many years to fully appreciate the heterogeneity of epilepsy syndromes that result from pyridoxine dependency states [26,27]. As a prototype for other epileptogenic diseases, pyridoxine dependency illustrates the principle that discordance between current syndromic classifications of epilepsy and the neurobiology of epilepsy is more often the rule than the exception. For many genetic or congenital epilepsies the age of onset, not a specific epileptic syndrome, is the characteristic feature (Table 1.4).

Initially, pyridoxine dependency was felt to cause only neonatal seizures and drug-resistant neonatal status epilepticus. However, over time the spectrum of epileptic disorders that are attributable to pyridoxine dependency expanded to include epilepsies with onsets ranging from *in utero* to early childhood. Many types of seizures and epileptic syndromes resulted. Seizure types included partial,

Table 1.3 International League Against Epilepsy (ILAE) classification of epilepsies and epileptic syndromes.

Localization related (focal, local, partial epilepsies and syndromes)

Idiopathic (with age-related onset)
- Benign childhood epilepsy with centrotemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

Symptomatic epilepsy
- Chronic epilepsia partialis continua of childhood (Kojewnikow's syndrome)
- Syndromes characterized by seizures with specific modes of precipitation

Cryptogenic

Generalized epilepsies and syndromes

Idiopathic (with age-related onset – listed in order of age)
- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

Cryptogenic or symptomatic (in order of age)
- West syndrome (infantile spasms, Blitz–Nick–Salaam–Krämpfe)
- Lennox–Gastaut syndrome
- Epilepsy with myoclonic–astatic seizures
- Epilepsy with myoclonic absences

Symptomatic

NON-SPECIFIC AETIOLOGY
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression burst
- Other symptomatic generalized epilepsies not defined above

SPECIFIC SYNDROMES
- Epileptic seizure may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature

Epilepsies and syndromes undetermined whether focal or generalized

With both generalized and focal seizures
- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spike–wave patterns during slow-wave sleep
- Acquired epileptic aphasia (Landau–Kleffner)
- Other undetermined epilepsies not defined above

Without unequivocal generalized or focal features: all cases with generalized tonic–clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization related, such as in many cases of sleep-grand mal (GTCS) that are considered not to have unequivocal generalized or focal features

Special syndromes

*Situation-related seizures (*Gelegenheitsanfälle*)*
- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycaemia

GTCS, generalized tonic–clonic seizures.
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Table 1.4 Epilepsy syndromes by age of onset and related conditions.

Neonatal period
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara's syndrome
Infancy
Migration partial seizures of infancy
West syndrome
Myoclonic epilepsy of infancy
Benign infantile seizures
Dravet's syndrome
Myoclonic encephalopathy in non-progressive disorders
Childhood
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic–astatic seizures
Benign childhood epilepsy with centrotemporal spikes (BCECTS)
Late-onset childhood occipital epilepsy (Gastaut)
Epilepsy with myoclonic absences
Lennox–Gastaut syndrome (LGS)
Epileptic encephalopathy with continuous spikes and waves during sleep (CSWS) including Landau–Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Progressive myoclonus epilepsies (PME)
Less specific age relationship
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
Familial temporal lobe epilepsies
Mesial temporal lobe epilepsy with hippocampcal sclerosis (MTLE with HS)
Rasmussen's syndrome
Gelastic seizures with hypothalamic hamartoma
Special epilepsy conditions
Symptomatic focal epilepsies not otherwise specified
Epilepsy with generalized tonic–clonic seizures only
Reflex epilepsies
Febrile seizures plus (FS+)
Familial focal epilepsy with variable foci
Conditions with epileptic seizures that do not require a diagnosis of epilepsy
Benign neonatal seizures (BNS)
Febrile seizures (FS)

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multifocal, hemiclonic, infantile spasms, myoclonic and generalized convulsive seizures in infants and young toddlers [28]. The syndromes include uncategorized encephalopathic disorders with partial and generalized seizures along with West syndrome and Lennox–Gastaut syndrome [29–31]. Furthermore, some cases of infantile and early childhood-onset epilepsy caused by pyridoxine dependency respond temporarily to antiepileptic drugs [32,33]. Inadequately treated pyridoxine dependency has been linked to progressive brain atrophy and catastrophic neurological outcomes [34,35].

Contemporary genetic discoveries have further emphasized that individual genetic mutations can result in variable clinical phenotypes. For example, a single gene mutation that causes the syndrome of generalized epilepsy with febrile seizures plus (GEFS+) produces different epileptic syndromes, some benign and some severe, even in different members of the same family [36]. The relationships between epileptic genotypes and phenotypes is to a large extent unpredictable. Moreover, variability in the genotype–phenotype relationships operates in both directions. A single epileptic genetic mutation can often result in different types of epilepsy and a single type of epilepsy sometimes can have different genetic origins. Individual genetic profiles will soon become available as a result of high-throughput diagnostic susceptibility gene testing, but will require astute and knowledgeable clinicians for accurate interpretation. However, environmental exposure and injury also influence the form of the epilepsy and, as a result, the classification of epilepsy will continue to be difficult.

The lessons illustrated by pyridoxine dependency, chromosomal disorders and single-gene disorders that cause 'pure' epilepsy point to the difficulties and invalidity of syndromic classifications. As pointed out by several authorities, syndromes lack clear limits and the boundaries are continuing subjects of debate [37]. In many cases syndromes serve better as descriptive after-the-fact categories of outcomes than as diagnostic entities on which to base prognosis.

Despite their often limited neurobiological validity, syndromic diagnosis is clinically useful. The value of classifying syndromes, as with classifying seizure types, lies in the use of a standard lexicon, which facilitates communication among professionals as well as lay persons. In some cases, syndromic classification provides a basis for fashioning symptomatic treatments. Using a seizure to comprehend aetiology or pathophysiology is similar to trying to guess what is funny from a smile. Standardized, the terminology used for epileptic outcomes for clinically similar groups underpins effective dialogue about the clinical epiphenomena that are being observed. However, the highly variable relationships between aetiologies and epileptic phenotypes suggest that a highly detailed, intricate classification may be futile. To summarize, both seizures and syndromes are symptoms of underlying brain disorders. Both are empirical and descriptive, not aetiological or physiological. As a general rule, individual syndromes have many different aetiologies and mechanisms.

Methods of epilepsy syndrome classification

In classifying the epilepsies, the major division depends on whether the principal seizure type is focal and has localized onset or is generalized. The second axis of categorization is aetiological; is the disorder symptomatic, idiopathic or cryptogenic? Symptomatic epilepsies, also called secondary epilepsies, are those caused by known brain disorders. Cryptogenic epilepsies are those in which a cause is presumed but not identified. Idiopathic epilepsies have no apparent cause, but are believed to be due to 'hereditary predisposition' [38]. In other words, they are thought to be genetic. Defining characteristics of idiopathic epilepsies include age of onset, clinical features, plus characteristic EEG patterns from both interictal and ictal recordings.

The associated clinical features that have been used to define the epilepsies are listed in Table 1.5. Among these, intellectual capacity and motor function and natural history merit special emphasis. Certain syndromes include mental retardation in a high proportion of affected people. When mental subnormality is a key component of a syndrome, the intellectual deficit can either antedate the appearance of epilepsy or develop only after chronic epilepsy with numerous seizures. Conversely, in some syndromes, normal intellect is an expected feature.

Table 1.5 Factors used to characterize the epilepsies or epileptic syndromes.

Seizure type
EEG patterns – both ictal and interictal
Age of onset and remission
Natural history
Associated clinical features
Familial predisposition
Response to or aggravation by specific medications

Table 1.6 Features of frontal lobe seizures.

Brief duration
Complex partial with little or no postictal confusion
Rapid secondary generalization
Prominent tonic or postural movements
Frequent complex gestural automatisms at onset
Frequent falling when discharges are bilateral

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Other factors that appear to affect the evolution of epileptic syndromes include treatment(s), the timing of treatment and the response to treatment. Each can contribute to the eventual clinical syndrome individually and in concert with other factors. Of course, when information about the current clinical picture is incomplete or erroneous the classification can be mistaken. Nonetheless, once syndromic diagnoses are established, 80% hold up over time [39].

The major groupings in the current classification of epilepsies have been validated consensually. In various studies, between one-third and close to all cases of new-onset epilepsy have been categorized according to the 1989 international classification [39–47]. In one study in which patients were reclassified 2 years later, classifications changed in 14%; 4% of changes resulted from evolution of the syndrome and 10% of relabelling resulted from acquisition of new information [17,21,45,48].

There are several impediments to diagnosing epileptic syndromes. When seizures first appear the clinical picture is often incomplete [39,49]. Consequently, some syndromes become discernible only over time after the disorders evolve a sufficient number of features to become distinctive and diagnosable.

Nowhere is the importance of time for sufficient development of distinctive clinical features more apparent than with encephalopathic childhood epilepsies such as infantile spasms and Lennox–Gastaut syndrome. These disorders materialize from a wide variety of premorbid conditions, arising in normal as well as compromised children. Similarly, many epilepsies that evolve into severe epileptic syndromes begin innocently as febrile seizures or occasional idiopathic generalized tonic–clonic convulsions in early childhood.

Localization-related (focal, local, partial) epilepsies and syndromes

In addition to the extensive classification of syndromes presented in the 1989 classification, the authors also described four anatomically defined localization-related epilepsies: temporal lobe, frontal lobe, parietal lobe and occipital lobe. These anatomical groups are considered next, with the major features of each group briefly listed. Localization-related syndromes account for approximately 60% or more of the epilepsies [20,44–46]. In children with epilepsy, 23% are idiopathic and 77% are symptomatic or cryptogenic.

Temporal lobe epilepsies

- Simple partial seizures with autonomic, psychic or certain sensory manifestations include epigastric rising, olfactory and auditory sensations or illusions.
- Complex partial seizures usually lasting more than 1 min, beginning with initial motor arrest followed by oro-alimentary and other automatisms. Other features are amnesia regarding the episode, postictal confusion and gradual recovery to normal.
- Seizures occur in clusters or in isolation.
- Interictal EEG features range from normal to abnormal with various irregularities including spikes, sharp waves, or slowing localized, but not restricted, to the temporal lobe region.
- Ictal EEG abnormalities include appropriately localized alteration of background rhythms, low amplitude, fast activity, spikes or rhythmic slow activity.

The temporal lobe syndromes were further subdivided into two groups: medial basal (amygdalo-hippocampal) and lateral temporal (neocortical). Symptoms pointing to the former location include rising epigastric discomfort, autonomic signs such as pallor, flushing, mydriasis, irregular respiration or respiratory arrest, abdominal borborygmi, eructation, plus fearful, olfactory and gustatory auras. Symptoms of lateral temporal seizures included auditory and/or visual sensory experiences, psychic dreamy states and dysphasias if the speech areas in the dominant temporal lobe were involved.

Frontal lobe epilepsies

Frontal lobe epilepsies are prone to misdiagnosis as psychogenic episodes. They manifest as simple partial, complex partial and partial secondarily generalized seizure types. As defined in the 1989 classification, the notable features of frontal lobe seizures are summarized in Table 1.6.

When seizures originate in specific areas of the frontal lobes they produce symptoms that reflect the normal functions that are mediated by that region. Thus, clinical features of seizures provide clues as to which area(s) of cortex are involved. Many seizures that originate in the frontal lobes are complex partial. However, in frontal lobe epilepsy, rapid spread makes localization on the basis of symptoms much less reliable than with temporal lobe epilepsy.

- Supplementary motor seizures result in fencing postures, focal tonic movement, speech arrest, vocalization.
- Cingulate seizures are complex partial and include affective and autonomic changes plus gestural automatisms.
- Anterior frontopolar seizures include psychic features, and adversive head and eye movements, and tend to cause abrupt loss of consciousness.
- Orbitofrontal seizures begin with motor or gestural automatisms, olfactory symptoms and autonomic signs.

- Dorsolateral frontal seizures are tonic or clonic with eye and head deviation and speech arrest.
- Opercular frontal lobe seizures involve taste, speech and oral–buccal movements. Auras attributed to this area include fear plus gustatory, laryngeal and epigastric sensations. Motor features include chewing, swallowing, speech arrest or clonic facial twitching. Salivation and other autonomic features are produced by seizures from this region.
- Motor cortex seizures tend to be simple partial and reflect the physiological role of the cortex that is producing the seizure. If after the seizure a postictal, so-called Todd's, paralysis occurs, it is an important clue that the seizure originated in the motor area.

Parietal lobe epilepsies

Seizures that originate in the parietal lobe are often sensory at the onset with variable secondary generalization and infrequent evolution to complex partial seizures [38]. Thus, the sensory components may be discretely localized or spread to contiguous areas. Sensations that have been described are mostly tactile and include tingling, electricity, crawling, stiffness, cold or pain/unpleasant dysaesthesias. Visual hallucinations of parietal origin are usually structured. Partial seizures originating in the parietal lobes have variable tendencies to secondarily generalize. Postictally transient neurological deficits that follow parietal lobe seizures are typical of the signs and symptoms that result from permanent parietal damage of other causes. These include asomatognosia, cortical sensory deficits, spatial disorientation and dyscalculia [38].

Occipital lobe epilepsies

Like parietal lobe seizures, when seizures originate in the occipital lobes, they reflect the usual function of that brain region and often involve eye movements, head turning and/or visual hallucinations [38]. Hallucinations that are generated posteriorly tend to be unstructured lights, colours and flashes whereas anterior occipital and temporal–occipital regions generate more structured images or visual distortions such as macropsia or micropsia. Depending on the areas of cortical involvement, visual abnormalities may be restricted to discrete portions of the visual fields.

Idiopathic localization-related epilepsies

Benign partial epilepsy of childhood

The syndrome of benign partial epilepsy of childhood (BPEC) is also called benign rolandic epilepsy (BRE) and benign epilepsy of childhood with centrotemporal spikes (BECTS). The natural history is favourable for normal neurological and cognitive function plus eventual remission of epilepsy in more than 97% [50]. It is characterized by the onset of usually infrequent partial seizures between ages 3 and 13 years. The temporal distribution of seizure favours nocturnal occurrence but seizures can occur at any time of day [51]. An autosomal dominant variant has been described [52]. Prior febrile seizures occur in 10% or less, and family history of seizures of various types in 40%. According to some physicians, half of these cases do not warrant treatment [53].

Although patients with BPEC are typically lesion free, findings that have been reported in patients who manifest the phenotype include hippocampal atrophy [54], cortical dysplasia [55], lesions of corpus callosum, porencephalic cysts and toxoplasmosis [56]. Of course, once a lesion is found, the diagnosis of BPEC usually needs to be changed.

The distinctive seizure type is simple partial, often with onset in the face and orobuccal area, variably followed by secondary generalization. The ictus may be sensory or motor or a combination of the two. Ictal phenomena include clonic jerking, speech arrest, drooling and unilateral tonic or clonic convulsions, or merely episodic dysarthria and drooling [57,58]. In most cases, consciousness is preserved until the seizures secondarily generalize [59]. Typically, examination is normal whereas the EEG is demonstrably abnormal owing to focal spikes that originate most often in the centrotemporal regions, although on repeated EEG recordings, the spikes often wander [60]. When centrotemporal spikes are discovered incidentally in EEGs of children who have not had seizures, most of the children do not go on to have seizures subsequently [61]. In approximately 25% of cases, the EEG occasionally reveals generalized spike–waves [62].

Although the natural history of typical BPEC is for remission of epilepsy and normal development [63,64], numerous reports describe children whose courses deviate from a benign pattern in terms of seizure frequency, seizure severity and occurrence of neuropsychological problems [65–68]. Fejerman *et al.* [69] described 26 children who had atypical evolutions of their epilepsies after presenting with typical clinical pictures of BPEC: 12 developed atypical benign partial epilepsy; three developed acquired epileptic aphasia (Landau–Kleffner syndrome); seven had bouts of status epilepticus; and five evolved mixed pictures of these atypical patterns.

The overlap of BPEC with other epileptic syndromes of childhood illustrates how the boundaries between syndromic entities are blurred and often indistinct. Some cases that present as BPEC evolve into more complicated clinical problems blending into phenotypes overlapping with Lennox–Gastaut syndrome, Landau–Kleffner syndrome and electrical status epilepticus during slow-wave sleep (ESESS) [70–72]. Cases have been labelled atypical benign partial epilepsy (ABPE) or pseudo-Lennox syndrome. Atypical features include bouts of status epilepticus, atypical absence seizures, atonic seizures [69,73] and cognitive and behavioural impairment combined with an EEG pattern of slow spike–wave – all of this along with the core feature of partial seizures. Some investigators have correlated the occurrence of cognitive impairment in BPEC with the abundance of paroxysmal EEG activity [74].

Benign partial epilepsy in infancy

Benign partial epilepsy in infancy, as first described by Watanabe *et al.* in 1987, consists of complex partial seizures appearing in infancy with normal interictal EEG patterns awake and asleep [75]. Subsequently, infants were identified who had both complex partial seizures and secondarily generalized seizures in various combinations [6,76], and, later still, cases were found with vertex spike–wave patterns during sleep [77]. Among those who had developed normally up to the age of 2 years, 90% continued to develop normally when evaluated at age 5 [78].

Childhood epilepsy with occipital paroxysms

Described by Gastaut in 1950, this disorder has prominent occipital epileptiform spike–wave activity that appears after eye closure and is suppressed by eye opening [79,80]. Clinical features include visual symptoms, such as hemianopsias and amaurosis, abstract and complex structured visual hallucinations along with seizures (simple and complex partial, and/or generalized convulsions) and prominent postictal symptoms with migraine headaches accompanied by nausea and vomiting. Subsequent reports indicated that the original cases described by Gastaut were rare and atypical. More typically, features may include severe epilepsy, epilepsy confounded by cognitive difficulties and lesional/symptomatic aetiologies that, in some cases, for instance with mitochondrial encephalopathy with lactic acidaemia and stroke (MELAS), are progressive [81]. These exceptions not withstanding, authoritative opinions regarding this condition emphasized an excellent prognosis. Some of the occipital lobe patients have progressive, degenerative aetiologies – whereas patients with benign rolandic epilepsy virtually never have progressive aetiologies. Key features include onset of episodic vomiting, eye deviation and impaired consciousness with variable secondary generalized convulsions at around 5 years of age. Most seizures are nocturnal. Most affected children have occipital spikes on EEG, but 20% may have spikes elsewhere or not at all [82].

Reading epilepsy

This rare, benign, non-progressive syndrome is characterized by reading-provoked sensorimotor symptoms affecting the oral–buccal–lingual–facial muscles that are involved in reading aloud [83]. However, reading aloud usually is not required to trigger the seizures. As a result, some authorities have recommended renaming the condition language-induced epilepsy [84]. The condition is accompanied by a positive family history of a similar disorder in as many as one-quarter of cases. Described by observers as myoclonic, jerking or tonic movements of the jaw, patients report sensations such as stiffness, numbness or tightness during the seizures. This is a pubertal or postpubertal disorder, with average age at onset being 17 years, with symptoms starting as young 10 years of age in some people [85]. Cases have been described that overlap clinically with BPEC, with juvenile myoclonic epilepsy and with absence epilepsy [86–88]. Some authorities feel that this is part of the idiopathic generalized epilepsy spectrum while others consider it to be a partial reflex epilepsy. Both may be correct as the behaviour can occur in either context.

Symptomatic localization-related epilepsy

There are many causes of symptomatic epilepsy and most lead to localization-related forms of epilepsy. These are considered further in Chapter 3; however, one condition, epilepsia partialis continua, is considered here because of its distinctive clinical presentation.

Chronic epilepsia partialis continua of childhood

Chronic epilepsia partialis continua of childhood (Kojewnikow's syndrome) is linked to two variants of epilepsia partialis continua (continuous partial seizures) and received special mention among various motor seizures in the 1989 classification [38,89,90]. The first type is characterized by a stable neurological picture that is punctuated by infrequent bouts of epilepsia partialis continua that are not linked to progressive brain disease. The second type is linked to progressive diseases caused by various progressive aetiologies. The clinical picture is one of progressive loss of motor and eventually mental function that follows prolonged periods of epilepsia partialis continua. In these cases the localization of the partial seizures migrates, leaving in its wake paralysis of the affected areas [91]. Rasmussen's encephalitis is one cause of the progressive form. A wide variety of aetiologies have been linked to Kojewnikow's syndrome including neoplasia, inborn errors of metabolism (cytochrome C oxidase-induced Leigh's disease) [92], immunoallergic paraneoplastic syndromes [93] and infections [94–96].

Generalized epilepsies and syndromes

Idiopathic generalized epilepsies (with age-related onset)

Benign neonatal familial convulsions

Although most seizures in the neonatal period are symptomatic of perinatal problems, especially hypoxia and ischaemia, idiopathic benign seizures rarely occur in otherwise normal, full-term newborns. Cases occur on both a familial and sporadic basis [97,98].

Inherited in an autosomal dominant pattern, benign familial neonatal seizures typically appear in the first 2 weeks of life [99,100]. The most common semiology is a generalized tonic phase followed by variable patterns of clonic and autonomic activity [101,102]. Approximately 10% develop subsequent epilepsy [103].

In the 1990s the disorder was linked to mutations in two genes (*KCNQ2* and *KCNQ3*) which determine the structure and function of potassium channels and hence influence brain excitability [104]. Other genetic causes are likely to be found.

Benign neonatal convulsions

Also called fifth-day fits, benign neonatal convulsions appear in previously normal newborns [99,104]. Seizure types include apnoeic, partial or generalized clonic, but not tonic. EEG interictal patterns include normal, focal or multifocal spikes and bursts of theta activity in the central regions, the so-called theta pointu alternant. Ictal patterns are mainly rhythmic spikes or rhythmic slow waves [104]. The typical picture is clusters of seizures of 1–3 min in duration, which occur for 24–48 h and then cease. During the cluster of convulsive activity, the seizures are said to be resistant to antiepileptic drugs. For the majority of affected newborns the natural history includes normal development and permanent remission of seizures. However, approximately 10% of newborns have ongoing problems. A few are delayed developmentally, have febrile seizures and/or have persistently epileptiform EEGs. North *et al.* [105] noted that in Australia the syndrome of fifth-day fits was 'epidemic' during the 1970s but disappeared thereafter.

Benign myoclonic epilepsy in infancy

This rare condition appears in infancy in normal children although symptomatic cases have been reported. Features include general-

ized axial, massive myoclonic seizures, interictal EEG pattern of generalized spike waves and a mixed picture developmentally. Persistent uncontrolled seizures are associated with developmental stagnation and psychomotor retardation. It is unclear if this is a phenotypic variant of severe myoclonic epilepsy of infancy (see below) [106,107].

Childhood absence epilepsy (pyknolepsy)

Childhood absence epilepsey (pyknolepsy) appears with the onset of absence seizures in the early and middle years of childhood. This disorder is characterized by female predominance, and affected individuals are usually of normal intellect; there is at least a 40% chance of remission. The absence seizures are quite brief, so brief that, in some cases, they go unrecognized as seizures for long periods. The seizures also tend to occur in clusters. Although absence seizures are the predominant seizure type, other types of seizures occur infrequently. The classical EEG pattern is monotonous, a generalized 3-Hz spike–wave. Clinically, this condition overlaps with several others, especially juvenile myoclonic epilepsy [108]. In a series of 194 patients with typical clinical features and a typical EEG, approximately one-third also had generalized tonic–clonic seizures at some point, and absence status occurred in 15%. When followed up after the age of 18 years, approximately 20% were still having seizures [109].

In population-based studies, absence epilepsies account for less than 3% of newly diagnosed seizure disorders, whereas in paediatric populations they account for 15–20% [40,41,43,110]. Although children with absence epilepsies as a group have an above average intelligence quotient (IQ), in some studies [111] some investigators have found an over-representation of academic and behavioural problems associated with childhood absence epilepsy [112]. As suggested originally by Metrakos and Metrakos [113], childhood absence epilepsy is generally felt to be inherited as an autosomal dominant disorder with variable penetrance.

Boundaries in generalized epilepsies that appear in adolescence are indistinct, suggesting underlying neurobiological relationships [114]. Olsson and Hagberg [115] identified two groups of children with absence epilepsy. Those in whom onset of seizures occurred before the age of 12 years responded to therapy quickly, had a low chance of generalized tonic–clonic seizures and had a high remission rate. On the other hand, juvenile onset after the age of 12 years was associated with a high risk of generalized tonic–clonic seizures and a high relapse rate after discontinuation of antiepileptic therapy. Both groups responded well to antiepileptic drug therapy. In up to one-third of patients with juvenile myoclonic epilepsy, epilepsy begins with absence seizures in early to mid-childhood – well before the peripubertal onset of myoclonic jerks that are diagnostic for juvenile myoclonic epilepsy [116]. When juvenile myoclonic epilepsy presents in this fashion with absence seizures and a 3-Hz spike–wave EEG pattern, it is impossible to differentiate from childhood absence epilepsy.

Many ion channel genes have now been implicated in absence epilepsy and other forms of generalized epilepsy (for a review, see ref. 117) and are too numerous to describe here.

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME), also known as impulsive petit mal or Janz's syndrome, includes the following: myoclonic jerks, general tonic–clonic seizures and absence seizures [118,119]. Initially thought to originate in the peripubertal period when the myoclonias usually appear, subsequent studies revealed that approximately 15–30% of people with the disorder experience the onset of absence seizures in childhood, in which case absence seizures always predate the appearance of myoclonic seizures [120–123]. Seizure precipitants include sleep deprivation, stress, alcohol intake and menses, with sleep deprivation being the most common and most important [124]. Interictal EEG patterns vary from a 3-Hz spike–wave to faster patterns of poly-spike–wave at 4–6 Hz; however, EEG patterns may be asymmetrical and misleading [122,125]. Photosensitivity is present in approximately one-third [125].

Juvenile myoclonic epilepsy often goes unrecognized or misdiagnosed. The most common source of these errors is the failure to identify the myoclonic jerks (myoclonias) that are required for the diagnosis or to misinterpret them as partial seizures [126]. Epileptic in origin, the myoclonias are accompanied by polyspikes and spike–wave EEG discharges. Although the jerks can be disruptive and numerous, occurring repeatedly over a period of minutes to hours, consciousness remains intact.

A notable feature of the jerks is that most patients do not report them voluntarily and may attribute them to early-morning clumsiness, nervousness or restlessness. This is surprising given that the jerks are often forceful and dramatic in form. For this reason, a history of myoclonias, especially after awakening, should be directly sought if JME is suspected in anyone who presents with generalized convulsions [127].

The typical natural history includes responsiveness to therapy with valproic acid and vulnerability to an exacerbation of seizures when treated with traditional antiepileptic drugs that modulate use-dependent sodium conductance, such as phenytoin and carbamazepine [128]. The prognosis for seizure control is excellent with medication. However, even if fully controlled, seizures often recur when medication is discontinued [129].

Epilepsy with grand mal seizures (generalized tonic–clonic seizures) on awakening

This condition overlaps considerably with other generalized epilepsies, especially with JME, in which most affected people also have generalized tonic–clonic seizures on awakening. The EEG pattern is generalized spike–wave [122]. Whether this syndrome represents a discrete entity or simply the leftovers from other disorders has been debated for years [130]. At best, the syndrome is indistinct because as noted in the 1989 classification 'If other seizures occur, they are mostly absence or myoclonic.' [38].

Cryptogenic or symptomatic generalized epilepsies (in order of age)

West syndrome (infantile spasms, Blitz–Nick–Salaam–Krämpfe)

The term 'infantile spasms' is used to describe a seizure type as well as an epileptic syndrome, an ambiguity that is avoided by the appellation West syndrome. Synonyms for infantile spasms include Blitz–Nick–Salaam–Krämpfe, massive myoclonic spasms, lightning spasms, flexion spasms, jackknife convulsions and infantile myoclonic epilepsy. West syndrome includes three

features: infantile spasms, developmental arrest and an EEG pattern of hypsarrhythmia.

The EEG is almost always abnormal in these patients [131]. Approximately two-thirds of patients have a pattern of hypsarrhythmia. One-third have focal abnormalities. Less than 2% of patients with infantile spasms have normal EEGs, and if the EEG is normal the diagnosis should be questioned. Young infants who have spasms without EEG paroxysms have an innocent condition called benign infantile myoclonus that does not require treatment [132]. Hypsarrhythymia is a severe epileptic EEG abnormality. There are 'mountainous' high-amplitude, asynchronous delta slow waves intermixed with multifocal spikes or poly-spikes and wave complexes.

The onset of infantile spasms occurs before age 12 months in 85% of cases, and spasms usually cease by age 5 years only to be replaced by other types of seizures [132–135]. In approximately 30% of cases other types of seizures, mostly partial, precede the spasms; in 40% of cases other seizure types appear after the spasms begin [134]. The ictal movements include mixtures of flexion and extension, purely flexor movements, or pure extension, which accounts for 22% of spasms studied by video-EEG monitoring In full form, flexor spasms cause flexion of the neck and trunk with adduction of the shoulders and outstretched arms and variable flexion of the lower extremities, so-called salaam fits. Males account for the majority of patients.

Spasms vary in intensity from subtle to dramatic forms. Often when they first appear they are subtle, but as the child grows older, they tend to become more intense and occur in clusters, during which the infant cries. The clusters are most common on awakening. Aggressive, effective treatment is believed to reduce the chance of developmental stagnation and subsequent retardation [136,137]. Currently, the optimal therapy of infantile spasms appears to be adrenocorticotropin hormone (ACTH), which is initiated within 1 month of the onset of the spasms or aggressive therapy with antiepileptic drugs [136–144].

The aetiology of West syndrome is diverse. In approximately two-thirds of cases the condition is symptomatic of identifiable brain disorders; in approximately one-third, the aetiology is idiopathic or cryptogenic. The most common aetiologies are perinatal asphyxia and tuberous sclerosis. However, any aetiology that results in brain malformation or brain tissue destruction can produce this epileptic picture. Idiopathic cases have the best prognosis [137].

Brain imaging is abnormal in 80% of children with West syndrome [144,145]. The most common abnormalities are atrophic lesions (50%), followed by, in order, malformations, atrophy plus calcification, calcifications and porencephaly. Occurring almost exclusively in females, Aicardi's syndrome includes agenesis of the corpus callosum, chorioretinitis, vertebral anomalies, cortical heterotopias and severe learning diffulties [146–148].

The prognosis in West syndrome is related to the underlying brain disorder and to the therapy [137,142,149]. Patients with idiopathic, cryptogenic infantile spasms who receive optimal therapy have the best prognosis; those with severe encephaloclastic disorders have the worst prognosis. Among all patients with West syndrome, 20% die before reaching the age of 5 years and between 75% and 93% have been reported to have learning difficulties; at least 50% have persistent epilepsy and one-half of these individuals develop Lennox–Gastaut syndrome.

Lennox–Gastaut syndrome

Lennox–Gastaut syndrome is an age-dependent syndrome that includes early childhood-onset epilepsy with either mental retardation before seizures start or developmental stagnation, leading to retardation that accumulates during the period that epilepsy remains uncontrolled [150,151]. The syndrome overlaps clinically with other severe myoclonic epileptic syndromes [152,153]. Approximately 25% of cases of Lennox–Gastaut syndrome evolve from infantile spasms or West syndrome [135,154].

In Lennox–Gastaut syndrome, tonic and atypical absence seizures are the most common seizure types, occurring in 71% and 49% of patients, respectively. Generalized tonic–clonic seizures (GTCSs) and astatic seizures (drop attacks) occur in approximately one-third of patients, whereas partial seizures occur in about one-quarter [155]. The distinctive interictal EEG pattern is a slow spike–wave with frequencies of 2.5 Hz. During sleep, bursts of 10-Hz activity occur.

Lennox–Gastaut syndrome shares many features with myoclonic astatic epilepsy, also called Doose syndrome [156]. Multiple seizure types typify both syndromes, and the evolution of the disorders, resulting in mental retardation when seizures are uncontrolled, is similar. Not surprisingly, there has been debate and confusion about the boundaries of Lennox–Gastaut syndrome and other myoclonic epilepsies with encephalopathy [153,157].

Epilepsy with myoclonic astatic seizures

This disorder is also called 'myoclonic astatic epilepsy of early childhood': it usually appears in children who were previously without any disorder. Even although it is listed here among cryptogenic or symptomatic conditions, it is an idiopathic disorder with a strong genetic component and a positive family history of epilepsy in more than one-third of patients [157]. The epilepsy usually starts with generalized tonic–clonic seizures occurring with or without fever. Over time, other seizure types appear. These include myoclonic seizures, astatic seizures (usually atonic), atypical absence seizures and generalized tonic–clonic seizures but not daytime tonic seizures. However, in Doose's 1992 report [158], 30% of 109 cases had tonic seizures, most of which were nocturnal. Minor motor status occurred in 36%. The EEG is abnormal owing to generalized patterns of spike and wave rhythms of 4–7/s and photosensitivity but not multifocal patterns [107,159,160]. The prognosis for normal development is related to the extent of seizure control. The risk of mental deterioration is increased by onset of epilepsy before the age of 2 years, bouts of minor motor status, tonic seizures, failure to respond to anticonvulsant therapy, and the failure to develop a normal alpha rhythm on the EEG. Children with persistent frequent seizures experience developmental stagnation that results in eventual learning difficulties.

Epilepsy with myoclonic absences

This uncommon disorder is characterized by absence seizures that are accompanied by dramatic bilateral myoclonic jerks that occur in synchrony with an EEG pattern of 3-Hz spike–wave. The onset

is during middle childhood, and a male predominance has been described [109,161]. Approximately one-half of the affected children have learning difficulties and karyotypic abnormalities are common [162]. However, in the absence of structural brain abnormalities, development may be normal [163].

Symptomatic generalized epilepsies and syndromes: non-specific as to aetiology (age-related onset)

The next four conditions overlap considerably phenotypically and share many aetiologies, including a wide range of inborn errors of metabolism and structural brain abnormalities, such as hemimegalencephaly and other disorders of neuronal migration. All are associated with a high risk of severe developmental impairment and persistent epilepsy and are generally resistant to treatment. As a group they support the general concept that the earlier the onset of symptomatic epilepsy, the more extensive the neuropathology is likely to be and the more grave the prognosis [164–166]. Taken collectively, these syndromes, which include early myoclonic encephalopathy, early infantile epileptic encephalopathy with suppression burst, West syndrome and Lennox–Gastaut syndrome, constitute a spectrum of age-dependent epileptic encephalopathies through which the severely epileptic child graduates from one syndrome to the next as brain maturation leads to evolving epileptic phenotypes [167].

Early myoclonic encephalopathy

With onset in the first 3 months of life, this syndrome results from various metabolic, malformative and encephaloclastic diseases that affect the brains of newborns. More than one-half of patients who manifest this severe epileptic phenotype do not live past 12 months [168]. If they do survive infancy, the clinical picture often evolves into infantile spasms or West syndrome. All affected infants present with profound developmental delay. The EEG shows a burst–suppression pattern [38]. As described by Aicardi [169], the seizures present as variable and erratic multifocal myoclonic jerks, but as the infants' brains mature, tonic spasms typical of West syndrome become predominant, only to be superseded by Lennox–Gastaut syndrome as the child ages.

Early infantile epileptic encephalopathy with burst–suppression

Beginning before the age of 6 months, this disorder is characterized by tonic axial spasms and burst–suppression EEG patterns. It is also known as Ohtahara's syndrome [167]. The same continuum of aetiologies produce this syndrome as produce early myoclonic encephalopathy, but tonic spasms rather than myoclonic seizures predominate in Ohtahara's syndrome [170]. For this reason, some regard this syndrome as an early-onset variant of West syndrome [171]. Often evolving into West syndrome, the seizures are therapy resistant and psychomotor retardation is the rule.

Additional idiopathic generalized epilepsies not yet codified by the ILAE

With careful clinical observations, additional epilepsy syndromes are being identified; one of these is Jeavons' syndrome, in which eyelid myoclonia is predominantly manifested and a characteristic EEG abnormality presents upon eye closure. The recognition of some of these epilepsy syndromes, reviewed in Panayiotopoulos [172], may be facilitated by the identification of specific genetic abnormalities that will simplify their diagnosis.

Epilepsies and syndromes undetermined whether focal or generalized

Neonatal seizures

Classification schemes for neonatal seizures and epilepsies do not conform to the same patterns as seizures and epilepsy in older patients. These are considered separately in Chapter 13.

Severe myoclonic epilepsy in infancy

First described by Dravet in 1978 [173], severe myoclonic epilepsy has its onset before the age of 1 year, when the patient presents with febrile convulsions, either generalized clonic or hemiclonic, that are often prolonged. Like fever, hot baths can also precipitate seizures in affected infants [174]. Prior to the onset of the epilepsy, development is normal but encephalopathy eventually develops [175]. After variable numbers of febrile seizures, afebrile seizures of various types appear. These include myoclonic seizures, either focal or generalized with concomitant EEG generalized spike–wave or poly-spike–wave patterns, atypical absence seizures, generalized tonic–clonic seizures and partial seizures in about one-half of affected children. Initially, the interictal EEG is normal but, over time, it becomes progressively epileptic with generalized fast spike–wave, focal and multifocal abnormalities. When severe, the myoclonic seizures cause the children to fall down and thus qualify for the descriptor astatic seizures. As seizure frequency increases, development stagnates, resulting in mental subnormality. Ataxia appears in half of these children [161]. The seizures continue despite aggressive therapy with antiepileptic medications and are associated with shortened life expectancy. Severe myoclonic epilepsy in infancy has been linked to mutations in the sodium channel gene *SCN1A* [176].

Several disorders have been described that are linked to severe myoclonic epilepsy of infancy because they evolve from febrile seizures and have mutations in the sodium channel gene. Collectively, the epilepsies have been named generalized epilepsy with febrile seizures plus (GEFS+) [177,178]. Other disorders, such as high-voltage slow-wave grand mal syndrome (HVSW-GM), overlap clinically, but whether the molecular pathogenetic mechanisms overlap remains to be determined [179]. Other clinically overlapping syndromes include early infantile epilepsy with generalized tonic–clonic seizures, cases of myoclonic astatic epilepsy and childhood absence epilepsy with generalized tonic–clonic seizures [180].

Epilepsy with continuous spike–waves during slow-wave sleep

This condition is defined by a continuous spike–wave EEG pattern during 85% or more of slow-wave sleep [181]. Synonyms and abbreviations include electrical status epilepticus during sleep (ESES) and continuous spikes and waves during slow-wave sleep (CSWS). The central features are cognitive and behavioural deterioration that follow the appearance of various types of epileptic seizures [182,183]. The types of seizures that have

been described include partial, absence, astatic and generalized tonic–clonic.

Several syndromic phenotypes have been described with ESES including typical Landau–Kleffner syndrome of acquired epileptic aphasia (see below) and frontal opercular syndrome, variants of benign partial epilepsy of childhood (BPEC) plus less discrete clinical pictures [184,185]. Some investigators feel that Landau–Kleffner syndrome and ESES represent the same condition [186]. Frontal opercular syndrome consists of episodic dysarthria, dysphagia, drooling and variable degrees of hand apraxia and hemi- or monomelic paralysis [187,188]. ESES occurs on both an idiopathic/cryptogenic and symptomatic basis, with several reports noting polymicrogyria and shunted hydrocephalus as causes [189,190].

Acquired epileptic aphasia (Landau–Kleffner syndrome)

Appearing in early childhood, usually before the age of 5 years, in previously normal children, the syndrome of acquired epileptic aphasia [191] presents abruptly or subacutely, with mutism, apparent deafness, behavioural abnormalities, an epileptiform EEG pattern and seizures in approximately two-thirds [38,192,193]. However, hearing is normal when evaluated by evoked response audiometry, pointing to verbal auditory agnosia as the proper diagnosis instead of deafness [194]. Multiple types of seizures occur, including partial, generalized tonic–clonic and absence seizures. Typically, the EEG is abnormal owing to generalized or multifocal spike and spike–wave patterns, although clinical investigations with positron emission tomography, magnetoencephalography and occasional electroencephalography studies point to temporal lobe dysfunction [195–197]. In sleep, continuous spikes and waves during slow-wave sleep are common. For this reason, some investigators have concluded that ESES and acquired epileptic aphasia represent a spectrum within the same condition [187]. The seizures tend to be resistant to drug therapy but abate with advancing age. Between 25% and 50% of patients experience much improved to normal language function when followed up in adolescence or later, but an EEG pattern of ESES lasting longer than 36 months [198,199] or persistently abnormal EEG patterns have been linked to continual language impairment [200,201].

Special syndromes: situation-related seizures *(Gelegenheitsanfälle)*

Febrile convulsions

Febrile seizures are the most common epileptic syndrome, occurring in more than 3% of children. Fever from any cause can provoke seizures in susceptible infants and toddlers. The seizures may be partial or generalized, brief or lengthy, single or repeated. Interictal EEGs are either normal or have non-specific irregularities. Following febrile seizures, the risk of subsequent afebrile seizures (epilepsy) is increased from two- to sevenfold in various studies [202–205]. Although heightened risk of later epilepsy has been linked to many historical and demographic factors in affected children, since 1995 genetic discoveries about the links between febrile seizures and later epilepsy have provided insight into the neurobiology of epilepsy. Various family members who are affected by the same, single point mutation may develop a heterogeneous array of epileptic syndromes [178,206].

Genetic studies in febrile seizures have identified several mutations that lead to febrile seizures and later generalized epilepsy, a group of disorders that has become known as generalized epilepsy and febrile seizures plus (GEFS+) [207]. Recently discovered causes of GEFS+ include mutations involving two genes for voltage-gated sodium channels (*SCN1A* and *SCN1B*) [208,209] along with mutations of the genes that encode the GABA-A receptor [210,211]. In addition, digenic inheritance has been described [212]. However, among familial GEFS+, mutations affecting *SCN1A* and *SCN1B* accounted for only 17% of cases, indicating that many more genetic mechanisms await discovery [213].

To date, most of the discoveries regarding inherited forms of epilepsy have resulted from investigations of families in which epilepsy occurs as the result of mutated genes that are inherited according to simple mendelian genetics. Berkovic and Scheffer [214] have estimated that 95% of genetic epilepsies are inherited in complex patterns owing to the combined effects of single or multiple genes that interact with environmental and experiential variables. Research endeavours involving thousands of well-characterized epilepsy patients will be required to fully understand the significance of both rare gene mutations and common gene polymorphisms in human epilepsy.

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2 Epidemiology and Prognosis of Epilepsy

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Epidemiological studies of epilepsy are important for many reasons, including the provision of fundamental information on the magnitude of the disorder, its causes and its consequences. They can also be used to quantify the impact of important variables, such as the risk for further seizures, the chance of becoming seizure free, and the risk of dying from seizures. Furthermore, they can identify factors that are associated with a low or high risk for intractability.

Prevalence studies of well-characterized epilepsy populations provide valuable information for planning purposes. How many have epilepsy? How many have mild or severe epilepsy? How frequent is epilepsy in different ages? How many have concomitant disorders, and of what type? This and related information make it possible to estimate the number affected individuals, the levels of care needed and the resources that will be required.

There are many sources for identifying epilepsy populations; these include diagnostic registries at hospitals and electroencephalogram (EEG) laboratories as well as registries of groups with conditions that increase the risk for epilepsy, such as mental retardation. When registries, which partly overlap, have identified the vast majority of persons with epilepsy in the study area, the study is considered to be population based (or community based) and thus representative of the general epilepsy population in the study area. The use of hospitals as the sole source for identification can bias the sample, resulting in an underestimation of the number affected and an overestimation of severe cases.

Epidemiological studies often categorize countries as developed and developing, based on such socioeconomic criteria such as level of industrialization and the presence of a mature market economy. This, of course, can be at times difficult and arbitrary. Furthermore, all countries change and are, in that sense, developing. In this chapter, countries in Europe, North America and Australia are classified as developed and the countries of Central and South America, Africa and Asia as less developed. Of course this is an oversimplification since some countries in the less developed parts of the world are socioeconomically more advanced than some of the more developed countries.

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General epidemiology

The size of the epilepsy population: prevalence

In order to compare the prevalence of epilepsy across different groups, the definition of epilepsy should be the same across studies. The definition recommended by international guidelines for epidemiological studies of epilepsy states that seizures should be recurrent (i.e. at least two seizures) and unprovoked by any immediate identified cause [1]. Epidemiological studies of epilepsy are mainly interested in active epilepsy, defined as a condition in which individuals with epilepsy have had at least one seizure during the last 5 years and/or are still being treated with antiepileptic drugs (AEDs).

More developed countries

Several population-based European studies that include all ages report that the prevalence of active epilepsy per 1000 population ranges from 6.2 to 7.6: in children it is generally lower, 3.6–5.3 (Table 2.1). In North America, studies from Rochester, Minnesota, report a prevalence per 1000 of 6.8 in 1980, the same as that reported from the southern states. A study on children and adolescents found a prevalence per 1000 of 4.7. Thus, the prevalence of epilepsy is similar in Europe and North America; prevalence in children is slightly lower (Table 2.1) [2–12].

Less developed countries

Studies from countries in South and Central America, Africa and Asia report larger differences in prevalence of active epilepsy than found in more developed countries [13–19]. Prevalence seems to be higher in South and Central America than in other parts of the world. Many of these studies are small but a large study also reported a high prevalence (Table 2.2) [13].

Several African studies report a high prevalence; many of these studies are small or include cases with provoked and/or inactive epilepsy. Larger population-based studies find prevalence similar to what is found in more developed countries (Table 2.2). The country in Asia where the largest number of studies has been carried out is India. There, a meta-analysis of 20 studies [18] found an overall prevalence per 1000 population of 5.3 with a 95% confidence interval (CI) of 4.3–6.4. Higher prevalence has been reported from other Asian countries (Table 2.2).

It is often claimed that epilepsy is more common in the less developed parts of the world. From the literature. this appears likely for South and Central America, possibly so for sub-Saharan Africa and less likely for Asia. From the age-specific prevalence,

Table 2.1 Prevalence of active epilepsy in more developed countries.

Country, year [ref.]	Prevalence per 1000 people		Age	No. of cases
	Not age-adjusted	Age-adjusted[a]		
Italy, 1983 [2]	6.2	6.7	All ages	278
Faeroe Islands (Denmark), 1986 [3]	7.6	7.8	All ages	333
USA, 1986 [4][b]	6.8	7.0	All ages	160
USA, 1991 [5]	6.8		All ages	383
Finland, 1989 [6]	6.3		Adults	1233
Sweden, 1992 [7]	5.5	5.7	Adults	713
Norway, 2000 [8]	5.3		Children 6–12 years	205
Sweden, 1996 [9])	4.2		Children 0–16 years	155
Finland, 1997 [10]	3.9		Children 0–15 years	329
Estonia, 1999 [11]	3.6		Children 0–19 years	560
USA, 1989 [12]	4.7		Children 0–19 years	1159

[a] Age-adjusted to the US population.
[b] Includes 22% with 'possible epilepsy'.

Table 2.2 Prevalence of active epilepsy in less developed countries.

Country, year [ref.]	Prevalence per 1000 people	Age	No. of cases
Chile, 1992 [13]	17.7	All ages	314
Bolivia, 1999 [14]	11.2	All ages	112
Ethiopia, 1990 [15]	5.2	All ages	316
Tanzania, 1992 [16]	10.2	All ages	185
Tunisia, 1993 [17]	4.0	All ages	141
India, 1999 [18]	5.3	All ages	3207
Pakistan, 1994 [19]	10.0	All ages	241

it can be estimated that globally more than 10 million children, close to 30 million adults and close to 3 million elderly have active epilepsy, a total of 43 million people. This means that children constitute one-quarter, adults two-thirds and the elderly 7% of the global epilepsy population. Of those with epilepsy, around 80% live in less developed countries. Since the largest population increase occurs in the elderly, both in more and less developed countries, it is expected that the elderly will constitute a growing part of the epilepsy population.

Gender

Most studies have found epilepsy to be more common in males [2–4,6,7]. However, there are exceptions. In a study from the USA covering a 50-year period, prevalence was higher for males between 1940 and 1970 but more common in females in 1980 [5]. The increase in prevalence of active epilepsy during the 50-year period was largely due to an increasing prevalence in females. Studies in children often report higher prevalence in males, but higher prevalence has also been found in females. Interestingly, the larger prevalence studies from South America report higher prevalence in females [14] or no difference [13]. In Asia most, but not all [19], studies report slightly higher prevalence in males. In Africa the situation is the same, with most [15,17], but not all [16], studies finding slightly higher prevalence in males. The difference in prevalence found between genders is rarely statistically significant [2,6], and in individual studies the dominance by females and males shifts between age groups. Thus, epilepsy probably is slightly more common in males but several studies find the opposite and therefore uncertainty remains as to whether there is a true gender difference in active epilepsy.

Ethnicity

Only a few prevalence studies have been conducted in racially heterogeneous populations and the effect of ethnicity is difficult to assess independent of socioeconomic factors. A study of childhood epilepsy in the USA found higher rates in the black than in the white population [12], restricted to children under the age of 10 years. In a population with all ages included, prevalence was higher in the black population, among both males and females, except for children aged 5 years or younger [4].

Socioeconomic factors

Using an index for material deprivation, a strong correlation was found between the prevalence of epilepsy and social deprivation in a study from Wales [20]. The correlation remained when patients with coexisting psychiatric illness or learning disability were excluded from the analysis. The authors considered whether social deprivation was a cause or a consequence of epilepsy and concluded that epilepsy was likely a consequence of social deprivation, because a high correlation with prevalence was found already in those under age 20 years, an age when the drift down the social scale as a result of epilepsy should be minor. Confirmation comes from an Icelandic study showing that low socioeconomic status is associated with an increased risk for developing epilepsy [21].

Seizure types

Modern epidemiological studies on seizure types have used the International Classification of Epileptic Seizures. However, this classification requires EEG and clinical data for accurate seizure typing and in many epidemiological studies this is not possible. For instance, many generalized convulsive seizures have a focal onset and rapidly generalize, precluding observation of focal onset. The results of these may be liable to error.

In more developed countries patients with partial seizures or localization-related epilepsies account for 33–65% of the epilepsy population, those with generalized seizures account for 17–60% and in 2–8% seizures are unclassifiable.

Studies in adults find that 55–60% have partial seizures (or localization-related epilepsies), 26–32% have primarily generalized seizures and 8–17% have seizures that are unclassifiable [6,7]. In studies of childhood epilepsy 36–66% have focal seizures/epilepsies, 30–62% have primarily generalized seizures and 2–4% have unclassifiable seizures [8,11,12]. Another study found that localization-related epilepsies account for 50% of the epilepsies in people under 40 years of age and account for 75% of epilepsy among people aged 75 years and older [5].

To summarize, partial seizures are more common than generalized seizures in both children and adults although the preponderance of partial seizures is more pronounced in adults. However, it should be remembered that many seizures categorized as generalized may have an occult focal onset. In less developed countries focal seizures account for 11–55%, generalized seizures for 26–86%, and unclassifiable seizures for 0–19% of patients [13–16,18]. Combining electroencephalography results with clinical diagnosis increases the proportion of seizures classified as partial from 20% to 26% in Ethiopia [15] and from 34% to 53% in Bolivia [14].

New cases with epilepsy: incidence

Incidence studies measure how many new patients develop epilepsy. The incidence rate is expressed as the number of new cases observed annually per 100 000 people (or 100 000 person-years). There can be a delay of months to years between the initial seizure(s) and contact with the health authorities and diagnosis. Thus, annual incidence rates provide information on newly diagnosed cases, whether or not the initial seizure(s) occurred prior to or during the investigation period. The index seizure is the seizure leading to the diagnostic contact. Some incidence studies of epilepsy include single unprovoked seizures. In studies on seizure prognosis it is important to be aware of whether the starting point is the time of the first seizure or the time of diagnosis.

Specific countries

In the USA, the UK, the Faeroe Islands, Sweden and Switzerland, annual incidence rates are around 50 : 100 000 [3,22–25] (Table 2.3). A study from Chile has reported the highest rate worldwide [13] (Table 2.3). The two existing studies on incidence of epilepsy from Africa report slightly higher incidence rates than found in more developed countries [16,26] (Table 2.3). However, when incidence is adjusted for age, using the US population, the incidence in Africa is similar to that found in more developed countries – around 50 : 100 000.

Age-specific incidence

Age-specific incidence forms a U-shaped curve, with the lowest incidence in people between the age of 30 and 40 years and the highest incidence in the elderly (Fig. 2.1) [3,22,25,27,28]. In the few studies from less developed countries, incidence is higher in children and (with a single exception) lower in the elderly than in more developed countries [13,16,26]. Globally, an estimated 3.5 million people develop epilepsy annually; 40% are children under the age of 15 years, another 40% are adolescents and adults 15–64 years old, and close to 20% are elderly. Thus, the majority of people who develop epilepsy do so after childhood.

Table 2.3 Annual incidence of epilepsy.

Country, year [ref.]	Incidence per 100 000 person-years	Age	No. of cases	Comments
Faeroes, 1986 [3]	43	All ages	118	
Sweden, 1996 [22]	56	Adults <16 years	160	SS included
Switzerland, 1997 [23]	46	All ages	176	SS included
UK, 2000 [24][a]	46	All ages	31	
USA, 1993 [25][b]	48	All ages	275	
Chile, 1992 [13]	113	All ages	102	
Tanzania, 1992 [16]	73	All ages	122	
Ethiopia, 1997 [26]	64	All ages	139	

SS, single seizures.
[a] Incidence 57 with SS[a] included.
[b] Data for the period 1975–84.

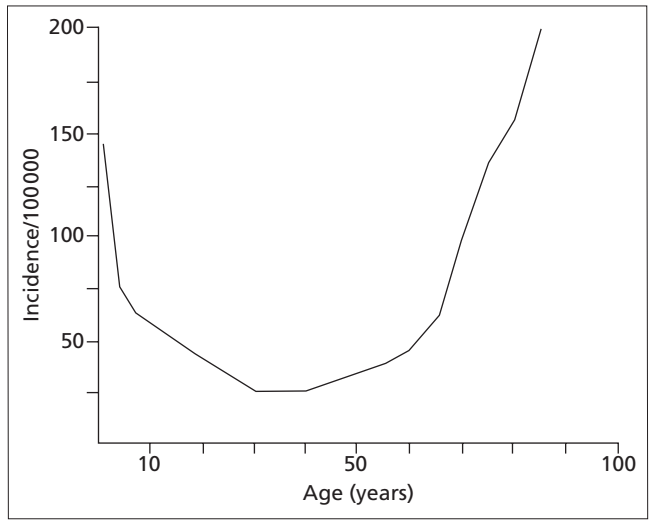

Fig. 2.1 Age-specific incidence of epilepsy based on studies from the USA, the Faeroe Islands and Sweden (single unprovoked seizures included in the Swedish studies) [3,22,25,27].

Cumulative incidence

The cumulative incidence is the summation of age-specific incidence and gives the proportion of a population that develops a disease during a specified period. In the USA, the cumulative incidence is 1.2% up to the age of 24 years, 3% up to the age of 74 years and 4.4% up to the age of 85 years [25]. When single unprovoked seizures are included, the cumulative incidence increases to 4.1% up to the age of 74 years. In Sweden,

the cumulative incidence up to age 74 years, with single unprovoked seizures included, was 4.1%, and 5.8% up to age 84 years [22]. Thus, approximately every 30th person is expected to have epilepsy during some part of his or her life, and every 25th person will have at least one unprovoked seizure.

Gender

Like prevalence studies, newly diagnosed epilepsy is more common in males than females, although the difference is rarely statistically significant [5]. Some studies find minor or no difference between gender and a few find a higher frequency in females.

Ethnicity and socioeconomic factors

In an incidence study in an urban area in the USA, new onset epilepsies were more common in black than white children [29]. Febrile and other provoked seizures, and neonatal seizures were included in the epilepsies. This study also reported an excess of epilepsy in both black and white children living in lower socioeconomic areas.

Seizure types in incidence populations

Partial seizures are most common and are found in 51–68% of incidence populations. In studies in which lower frequencies are found, the most likely explanation is that a proportion of partial seizures with secondary generalization was misclassified as generalized. Seizures were generalized in 16–69% and unclassifiable in 0–17% [3,13,25,26,28].

Causes of epilepsy

The aetiologies of epilepsy are best explored in population-based studies of newly diagnosed patients. Prevalence studies are less well suited for aetiological analysis, because several causes of epilepsy are themselves associated with increased mortality, and such epilepsies will be underrepresented in prevalence cohorts. Also underrepresented are individuals with the most benign epilepsies that rapidly enter remission.

The most commonly identified aetiology in all population-based studies from more developed countries is stroke, accounting for approximately every sixth patient who develops epilepsy (Table 2.4) [22,25,27,28,30]. Other common causes are neoplasm and congenital disorders. Congenital disorders mainly include patients with mental retardation, cerebral palsy and/or a developmental malformation of the brain. Other fairly common causes of epilepsy are trauma and degenerative disorders. The most common neurodegenerative disorder causing epilepsy is Alzheimer's disease, which causes generalized tonic–clonic seizures (GTCSs) in 10–16% of patients [31,32], predominantly during the late stage of the disease [32], at which point many also develop myoclonic seizures [31]. Partial seizures have also been reported in Alzheimer's disease.

In less developed countries, the proportion of patients with epilepsy with unknown causes is large, over 70%, in population-based incidence studies [26]. While the aetiologies of epilepsy are found in all countries, some aetiologies, for example head trauma, infections, pre- and perinatal causes, may be more common in less developed countries. In these countries, there are additional causes such as neurocysticercosis, an infection of the central nervous system (CNS) contracted by eating pork, fruits or vegetables contaminated by the pork tapeworm *Taenia solium*, which is endemic in South America, parts of Africa, India and China. In a study from Ecuador [33] on newly diagnosed patients with epilepsy, the proportion with identified causes was similar to more developed countries, but neurocysticercosis was found in 8% of these patients.

Table 2.4 Population-based studies estimating the proportion (%) of identified presumed causes of epilepsy.

Aetiology	Study				
	Iceland [28]	Sweden[a,b] [22,27]	UK[b,c] [30]	USA [25]	Range
Vascular	9	21	15	11	9–21
Ischaemia	18	–	–	–	–
Haemorrhage	3	–	–	–	–
Trauma	5	2	3	6	2–6
Neoplasm	6	7	6	4	4–7
Infection	1	0	2	3	0–3
Degenerative	6	5	–	4	4–6
Congenital	4	7	–	8	4–8
Other	1	4	13[d]	0	0–13
Remote or progressive symptomatic	33	46	39	35	33–46
Idiopathic/cryptogenic	67	54	61	65	54–67

[a] Frequencies based on combining studies on children and adults.
[b] Includes single seizures.
[c] Includes 15% with acute provoked afebrile seizures.
[d] Includes 6% with alcohol-related seizures.

Associated disabilities (co-morbidities)

Most people with epilepsy do not have other disabilities, but conditions that cause epilepsy often also produce other disabilities that may have a minor impact compared with epilepsy, or may be the major disability. Cognitive disabilities are more common than motor disabilities in studies of prevalent epilepsy. In newly diagnosed patients, however, motor disabilities are more common than cognitive disabilities.

Learning disabilities

Learning disability, also called mental retardation, is the most common associated disability in epilepsy in children and adults. Mental retardation is found in 38–49% of children [8] and in 23% of adults [7] with active epilepsy. Similar frequencies were reported from India, and in Ethiopia 8% were severely mentally retarded [15].

The degree of mental retardation is clearly related to the risk for epilepsy. Among children with mild mental retardation [intelligence quotient (IQ) of 50–70] epilepsy is found in 7–18% and among children with severe mental retardation (IQ < 50) in 35–44%. In a population with mental retardation including all ages, active epilepsy was found in 20%, corresponding to a prevalence of 1.2 per 1000 people [34]. This study also shows a clear relationship between the degree of mental retardation and frequency of epilepsy, with epilepsy occurring in 11% of the mildly mentally

retarded and 12% of moderate, 23% of severe and 59% of profoundly retarded individuals [34].

Cognitive disability is also found in people with epilepsy due to stroke or dementia. Among adults with newly diagnosed unprovoked seizures, 18% were demented [22].

Cerebral palsy

Cerebral palsy is common in patients with epilepsy: present in 15–21% of children and 9% of adults [7,8]. The vast majority, 89–100%, of children with epilepsy and concurrent cerebral palsy are also mentally retarded [8]. Likewise, the combination of mental retardation and cerebral palsy increases the risk for epilepsy to 48%, compared with 11% when either of these disabilities occurs alone [35]. Epilepsy is more frequent in the most severe form of cerebral palsy, tetraplegia, occurring in 94% of patients with tetraplegia compared with 23% of patients with hemiplegia.

Mental retardation and cerebral palsy should not be regarded as causes (or consequences) of epilepsy, as sometimes stated in the literature. Instead, any combination of these three disorders should, with a few rare exceptions, be considered as different manifestations of a prior brain insult, usually one that occurred early in life.

Seizure frequency

In unselected prevalent seizure populations, an estimated 40–50% have been seizure free during the last year, about 30% have up to one seizure per month and another 20–30% have seizures more frequently than once a month [7–10].

In patients with epilepsy and mental retardation, the proportion with very frequent seizures is much higher than in the general epilepsy population. About 10% have daily seizures and another 15% have one seizure or more per week, which means that one-quarter have at least weekly seizures [34].

Studies from less developed countries find a larger proportion of people with epilepsy having frequent seizures, probably largely because many patients do not receive treatment; studies in Ethiopia, for instance, find that less than 2% receive treatment, and from Bolivia only 11% [14,15]. Another contributory reason may be the underascertainment of patients with low seizure frequency.

Epidemiological time trends

Overall, the incidence of epilepsy was relatively stable in Rochester, Minnesota, USA, for a 50-year period [25,36]. However, age-specific incidence rates have changed significantly. The incidence in children younger than 10 years decreased successively by 40–50% between 1935 and 1984 with a slight increase during the last decade studied (1975–1984) [25,36]. The reason for this decrease is unknown but improved ante- and perinatal care may be partly responsible. Similar trends were observed in Sweden and the UK.

The study from Rochester also found an increase in incidence in those over the age of 60 years that almost doubled during the 50-year study period [36]. The secular trend with an increased incidence in the elderly may be a result of better survivorship from stroke, a group with increased risk for epilepsy, and also may be a result of more accurate case ascertainment.

Prognosis of seizures

Almost all studies on the prognosis of epilepsy published before 1970 were cross-sectional studies in hospital populations. These were biased by an overrepresentation of patients with severe epilepsy and the seizure prognosis observed was considerably worse than for general epilepsy populations. The Guidelines for Epidemiologic Studies on Epilepsy define epilepsy in remission as no seizures for 5 or more years [1]. Depending on whether the patient is receiving AED treatment or not at the time of ascertainment, remission is further specified as occurring with or without treatment. Terminal remission refers to patients still in remission at the end of a follow-up period. Temporary remission refers to patients in whom remission has occurred for a defined period earlier during the follow-up period, followed by a relapse. Permanent remission is not well defined but could be used for patients in terminal remission for a long period, for example 20 years, and judged to be very unlikely to relapse. The term could also be used for patients with specific syndromes with good prognosis once a certain age is reached, for example in patients with benign epilepsy of childhood with centrotemporal spikes (BECT) after the age of 18 years. Cumulative remission refers to the proportion that has been in remission at any time during the follow-up period, i.e. patients in both temporal and terminal remission. Some studies have used the term temporary remission for cumulative remission.

Early prognosis

The risk for a second seizure following a first unprovoked seizure has been investigated by several studies, discussed in detail in Chapter 10. When two unprovoked seizures have occurred, the person by definition has epilepsy. While a minority will have a second seizure following a first seizure, the proportion with a third or fourth unprovoked seizure following a second is considerably higher, 73% and 76%, respectively [37]. Seizure recurrence following a first, second or third seizure mainly occurs within 1 year [37].

Late prognosis: overall remission

In population-based studies of newly diagnosed epilepsy from more developed countries, the vast majority of patients are treated with AEDs. Thus, these studies give the prognosis of treated epilepsy and not the natural history of epilepsy. Results from studies are very similar despite some variation in methods (Table 2.5) [38–42]. At 10 years' follow-up, 5-year cumulative remission was 58–65% in studies from the USA and the UK including all ages [38–40] and from Sweden including adults [41]. Terminal 5-year remission at 10 years' follow-up was 61% [38]. Higher remission rates are found in children, of whom 74% achieve 3–5 years' remission at 12–30 years' follow-up [42]. In a prospective study with patients mainly collected by paediatric neurologists, 10% of children developed intractable epilepsy with more than monthly seizures during 18 out of the first 24 months following diagnosis [43]. The only study including all ages with a follow-up exceeding or of similar length as the childhood studies found a terminal 5-year remission rate of 70% at 20 years [38]. Fifty per cent were seizure free without antiepileptic treatment and 20% with treatment. Thus, at least 30% of patients will eventually achieve long-term remission, and about 75% of children.

Table 2.5 Population-based studies on epilepsy prognosis.

Country, year [ref.]	In remission (%)[a]	Years of remission	Follow-up (year)	Number followed	Age group	Comments
USA, 1979 [38]	65, 61	5	10	458	All	Incidence cohort, population based
	76, 70	5	20			
UK, 1995,97 [39,40]	86, 68	3	7	564	All	Incidence cohort, population based
	68, 54	5	7			
	82	3	7	397		SS and APS excluded
	62	5	7			SS and APS excluded
Finland, 1993 [42]	76	3	30	178	Child	Incident and prevalent
	74	5	30			
Sweden, 2001 [41]	64	3	10	107	Adults	Incidence cohort, population based, SS
	58	5	10			

APS, acute provoked afebrile seizures; SS, single seizures.
[a] First number refers to temporary remissions and second to terminal remissions.

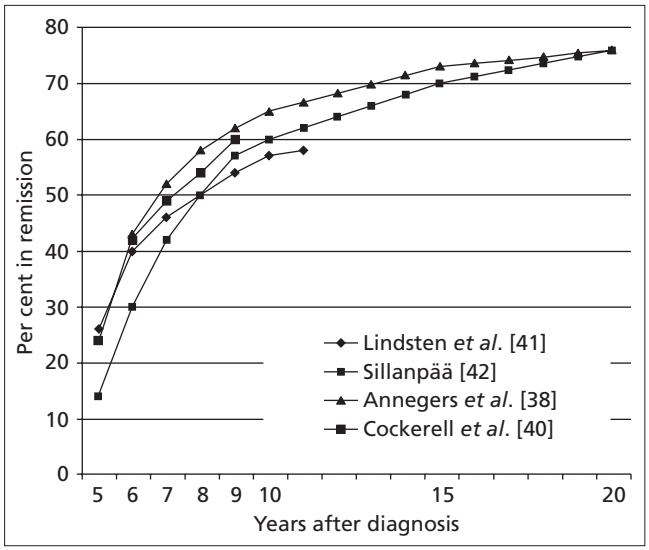

Fig. 2.2 Cumulative 5-year remission of epilepsy years after diagnosis. Population-based studies.

Time to enter remission

All studies on remission in newly diagnosed patients find that most patients enter seizure remission early, although one study has reported a waxing and waning of remission [44]. The longer patients continue to have seizures, the lower the probability for subsequent remission. Curves from studies depicting the relationship between remission and years after diagnosis have the same form with minor deviations (Fig. 2.2).

Initial seizure frequency

The seizure frequency during the first 6 months greatly affects the chance to achieve long-term remission. In the UK, 1-year remission by 6 years' follow-up was found in 95% of patients with up to two seizures during the first 6 months following diagnosis and in 75% of patients with 10 or more seizures during the same period [45]. The corresponding rates for 5-year remission by 6 years were 47% and 24%. In children, high initial seizure frequency also predicts the development of intractable epilepsy, defined as more than one seizure per month for at least 18 months, despite trials with at least three different AEDs during the first 2 years following diagnosis [43]. Only 12% of children achieved 1-year remission during a mean follow-up period of 38 months.

Predictors of seizure remission

Gender

Gender appears not to influence seizure prognosis [38,45].

Age at onset

Age at onset of epilepsy is not a significant predictor of remission. In Rochester, Minnesota, the proportion that achieved 10-year remission decreased with increasing age at onset [38]. Other studies found small or no effect [40].

Aetiology

Overall, idiopathic/cryptogenic epilepsy has a better prognosis than symptomatic epilepsy. Studies on aetiology as a potential predictor for seizure prognosis have used the term idiopathic/cryptogenic for cases with epilepsy of unknown cause. A study from Rochester, Minnesota, reported higher 5-year remission rates without medication for idiopathic/cryptogenic epilepsy (36% and 42% after 10 and 15 years, respectively) than in the remote symptomatic group (remission rates 19% and 30%) [38]. However, after 20 years, 5-year remission was slightly more frequent in the remote symptomatic group (54%) than in the idiopathic/cryptogenic group (47%), a change attributed to increased mortality in the remote symptomatic group leaving a subgroup with better prognosis. The difference was even larger at 20 years when all cases in remission (with and without medication) were included; 74% of the idiopathic/cryptogenic cases and 90% of the remote symptomatic cases were in remission for 5 or more years.

In a Finnish study of childhood-onset epilepsy, remote symptomatic aetiology was a predictor for seizure intractability [42].

Studies from the UK and Sweden did not find aetiology to be a significant predictor for remission, with more than 60% of both the idiopathic/cryptogenic and remote symptomatic groups achieving cumulative 5-year remission at 9 or 10 years' follow-up [39–41,45].

Co-morbidities

Mental retardation and cerebral palsy make up the vast majority of disorders in this group, with neurological dysfunction present since birth, often called the neurodeficit group or the group with early brain damage. This group has the worst prognosis for seizure remission. In Rochester, Minnesota, 5-year remission at 20 years was found in less than half (46%) of the study group; this was achieved without medication in only 15% and 30% at 10 and 20 years' follow-up, respectively [38]. In childhood-onset epilepsy the neurodeficit group also have less chance of achieving long-term seizure remission [42].

Specific aetiological factors

Stroke

Following stroke, acute symptomatic seizures (ASS) occur in 1.8% during the first 24 h [46] and in 4–6% during the first 1–2 weeks [47]. ASS should be classified as acute provoked seizures if they occur during the first week following stroke [1]. Most ASS, defined as acute provoked seizures that occur during the first week after the stroke, occur largely during the first 24 h in 78–87% of population-based studies [46,47].

By 5 years after a stroke, approximately 10–12% of patients will have seizures, either early, late or both [46,47]. Most patients with ASS do not go on to have late unprovoked seizures or epilepsy. At 5-year follow-up, 36% with ASS went on to have seizures whereas only 7% without ASS developed epilepsy [46]. Epilepsy is more common following a late seizure, found in almost 55–60% after ischaemic stroke. Early seizures do not predict 30-day mortality [46,47] when stroke severity has been accounted for. Status epilepticus occurs in one-quarter of stroke patients who have ASS [47].

The characteristics of the stroke affect the occurrence and prognosis of seizures. Haemorrhagic stroke more often results in seizures than ischaemic stroke. Population-based studies report ASS in 2–3% with ischaemic stroke, in 3–7% with haemorrhagic stroke and in 6–8% with subarachnoid haemorrhage (SAH) [46,47]. When ischaemic stroke patients were followed for 5 years the cumulative risk for seizures increased during the whole 5-year period and reached 10% [46]. After primary intracerebral haemorrhage and subarachnoid haemorrhage all seizures occurred by the third year, with a cumulative risk of 26% and 34%, respectively. ASS seizures as a result of stroke are mostly focal, but generalized seizures without obvious focal onset occur in one-quarter of patients [47] and were reported in 50% within 24 h of the onset of stroke [46].

Trauma

Seizures occur in 4–5% of patients with head trauma [48]. Late unprovoked seizures (late is defined as occurring more than 1 week after the insult) occur in 2% of patients: three-quarters of these will be recurrent, i.e. epilepsy [48]. Late seizures follow ASS in 10–15%, mostly in adults with moderate to severe head injury. In multivariate analysis, ASS do not predict late seizures [48].

The risk for seizures varies according to the severity of head trauma and time since head trauma. For all degrees of head trauma the elevated risk decreases with time. Mild head trauma (loss of consciousness or amnesia ≤30 min) results in a very minor increase for late seizures, which are only seen during the first 5 years following trauma [48]. Moderate head trauma (loss of consciousness or amnesia 30 min to 24 h, or skull fracture) causes a threefold increase in seizures compared with the general population during the first 10 years following trauma but not thereafter. Severe head trauma (loss of consciousness or amnesia >24 h, brain contusion or intracranial haematoma) increases risk 17-fold, and the increased risk persists beyond 10 years.

Central nervous system infections

Central nervous system (CNS) infections predispose to subsequent epilepsy that may appear many years later. In a population-based study of people with CNS infections followed up after an average of more than 10 years, ASS was observed in 19% [49], and by 20 years the cumulative risk for late unprovoked seizures was 7%. The majority, 58%, of late seizures occurred in patients with previous ASS. In 98% (all but one patient) late seizures were recurrent. Thus, prophylactic antiepileptic treatment is unwarranted in CNS infections and ASS, but should probably be started after a late unprovoked seizure.

Viral encephalitis with ASS carries the highest risk for later epilepsy, found in 10% by 5 years and 22% by 20 years' follow-up [49]. Without ASS, the cumulative risk of epilepsy after viral encephalitis is 10% by 20 years. The corresponding rates of epilepsy after bacterial meningitis are 13% with ASS and 2% without ASS, and 2% for aseptic meningitis at 20 years' follow-up. The low cumulative incidence of epilepsy following bacterial meningitis without ASS and following aseptic meningitis is no greater than expected in the general population [49].

Neurological deficits

Early brain damage causing neurodeficits is a strong predictor for long-term seizure prognosis. Studies have found neurological abnormalities to be associated with increased risk for persistent epilepsy. This has been substantiated in childhood-onset epilepsy [42] and in hospital-based studies of newly diagnosed cases.

Seizure type

By 20 years' follow-up, 5-year remission was found in 85% of patients with idiopathic/cryptogenic GTCS (50% off medication) and in 80% with absences, in Rochester, Minnesota [38]. A lower remission rate, of 65%, occurred in patients with complex partial seizures (CPS) (35% off medication) although the CPS figures may be low because of underascertainment of mild cases. At 20 years' follow-up, the highest remission rates, 77%, occurred in patients with generalized seizures and seizure onset before age 20 years. The lowest remission rate, 59%, was found in patients with PS and onset after age 20 years. In other studies seizure type was an inconsistent predictor for remission [40,41,43,45]. However, hospital-based studies on newly diagnosed cases have reported that multiple seizure types and partial seizures worsen long-term seizure prognosis.

Status epilepticus

In childhood-onset epilepsy followed for 30 years, status epilepticus (SE) is a predictor for not achieving remission [42]. Prior acute symptomatic or neonatal SE, but not unprovoked or febrile SE, predispose to the development of intractable epilepsy [43].

Electroencephalogram

The absence of generalized epileptiform activity on the first EEG was a significant predictor for cumulative 5-year remission (different analysis of data from reference 38). Whereas focal epileptiform activity and generalized non-epileptiform activity were not of prognostic value in children with epilepsy, focal slowing on the EEG was a predictor of intractable epilepsy [43].

Relapse after achieving remission

Relapse can occur despite achieving long-term remission, and a mean annual relapse incidence of 1.6% has been reported [38]. Relapse occurred in 8% during the first 5 years following 5-year remission and in 15% at 10 years after remission. By 20 years following remission almost one-quarter (24%) had relapsed. Relapse by 20 years is most frequent in patients with CPS (32%) and became more common with increasing age in this study. Relapses following 5-year remission occurred at diagnosis in 13% of patients aged 9 years or younger, in 22% of patients aged 10–19 years, and in 32% and 45% of patients aged 20–59 years and 60 years and above, respectively [38]. Recurrence of seizures is common when AEDs are discontinued, often necessitating treatment for several decades or lifelong [50].

Mortality

Measures of mortality

Mortality rate is the number of deaths during a specified period divided by the number of persons at risk of dying during the period. Studies on mortality rates in epilepsy often use death certificates to identify deaths related to epilepsy.

Mortality in epilepsy is often expressed as the ratio between the observed and expected numbers of death – the standardized mortality ratio (SMR). Expected deaths are calculated by applying the death rates of a reference population to the age distribution of to the study population. When there is no difference in mortality between the study and reference population the SMR is 1; a 95% CI that includes 1 indicates that the SMR is not statistically significant. The SMR cannot be compared between studies when age distributions and age- and sex-specific death rates differ.

Case fatality is the proportion of the cohort with epilepsy that dies over a specified time period: it is expressed as a percentage.

Overall mortality in population-based studies

Population-based studies of mortality in cohorts with newly diagnosed unprovoked seizures or epilepsy are shown in Table 2.6. Most studies included persons who presented with incident single unprovoked seizure [51–55]. SMRs in population-based studies vary from 1.6 to 4.1 (Table 2.6), which means that in unselected epilepsy populations the excess mortality is 60% to 310% of that in the control population without epilepsy.

Table 2.6 Standardized mortality ratios in population-based studies of epilepsy, by aetiology.

Country, year [ref.]	All (95% CI)	Idiopathic[a]	Aetiology	
			Remote symptomatic	Neurodeficit
USA, 1980 [51]	2.3 (1.9–2.6)	1.8 (1.4–2.3)	2.2 (1.8–2.7)	11.0 (6.9–16.4)
UK, 2001 [52]	2.6 (2.1–3.0)	1.3 (0.9–1.9)	3.7 (2.9–4.6)	25.0 (5.1–73)
Iceland, 1997 [53]	1.6 (1.2–2.2)	1.3 (0.8–1.9)	2.3 (1.4–3.5)	–
France, 1999 [54]	4.1 (2.5–6.2)	1.5 (0.4–3.9)[b]	6.5 (3.8–10.5)	–
Sweden, 2000 [55]	2.5 (1.6–3.8)	1.1 (0.5–2.4)	3.3 (2.4–4.5)	–
Range (SMR)	1.6–4.1	1.1–1.8	2.2–6.5	–

SMR, standardized mortality ratios.

[a] Includes cryptogenic.

[b] Includes all cases with seizures of unknown aetiology: idiopathic and cryptogenic.

Overall mortality in selected epilepsy populations

Mortality has also been studied in selected epilepsy populations, such as those with cancer, but the impact of selection bias results in a tendency to overestimate mortality in these studies. Generally, the SMRs in these selected populations are higher than in the general population and this may be partly because selected epilepsy populations contain more people with severe epilepsy than unselected general epilepsy populations.

Epilepsy mortality in less developed countries

No studies have specifically investigated mortality in epilepsy populations from less developed countries because standardized population mortality rates are less available for comparison. Case series in some countries, however, show that falls, burns, SE and drowning are the most common causes of death in these epilepsy populations. In Ethiopia, 20 patients out of 316 in a prevalence population with epilepsy died during an observation period of 2 years, with 45% of the deaths being seizure related, mainly SE [15]. The crude annual death rate was doubled in the epilepsy population compared with the general population of the study area [26].

Mortality by aetiology

In population-based studies, the mortality is lower in the idiopathic/cryptogenic group than in the remote symptomatic group (static encephalopathy) (Table 2.6). Most studies report little or no increase in mortality in the idiopathic/cryptogenic group [52–55]. In the remote symptomatic group mortality was two to six times greater than in the general population. The group with neurodeficits carries the highest mortality with SMRs of between 11 and 25 [51,52].

Mortality by age and gender

The majority of studies [51,53,55] report higher mortality in males than in females with epilepsy. Age is another factor

affecting the relative mortality. The relative mortality of epilepsy populations compared with reference populations is higher at all ages. Most studies have found an inverse relation between SMR and age. The highest SMRs are found in children, and decreasing SMRs are found with increasing age [51]. The high SMR in children and young adults with epilepsy is partly a reflection of two factors, the low mortality in the reference population and the high mortality in children with epilepsy and neurodeficits [51].

Although the highest SMRs are found in children, the highest excess mortality is found in the elderly. In the Rochester, Minnesota, study [51], the lowest excess mortality due to epilepsy, 6:1000, was found in children, in whom the SMR is highest [51]. The highest excess mortality, 47:1000, or eight times higher than in children, was found in the oldest age group, 75 years and older [51]. In Iceland, 81% of the study population had idiopathic/cryptogenic epilepsy. When mortality was analysed by age at onset of epilepsy, no increase in mortality was found in any age group with idiopathic/cryptogenic epilepsy [53].

Mortality by duration of epilepsy

The increase in mortality is most marked during the initial years following diagnosis [51–55] because of progressive pathologies. However, in longstanding epilepsy, mortality remains higher than that in the general population supporting the assumption that other determinants besides aetiology contribute to mortality. Seizure frequency and seizure severity could be some of these factors.

Mortality by seizure type

Generalized tonic–clonic seizures

A significantly increased mortality was reported from the USA for idiopathic/cryptogenic generalized tonic–clonic seizures (GTCS), with SMRs of 3.5 and 2.4 at 5 and 30 years, respectively, following diagnosis [51]. In Iceland, mortality was not increased in patients with idiopathic/cryptogenic GTCS without generalized spike–wave activity on the EEG (SMR 1.0) [53]. The use of EEG criteria in the Icelandic study excluded a large portion of the primary GTCS from the idiopathic/cryptogenic GTCS group. In Swedish males, with GTCS following either idiopathic/cryptogenic or remote symptomatic epilepsy, there was a statistically significant risk for death (SMR 3.9, 95% CI 2.3–6.8) [55]. Rates for GTCS in the cited studies are not fully similar owing to differences in inclusion [51,53,55].

Partial seizure with or without secondary generalization

Data regarding the relationship between partial seizure (PS) and mortality rates have been inconsistent. In some studies mortality was not significantly increased in patients with complex PS with or without generalization or in idiopathic/cryptogenic cases with PS (all types combined) [51,53]. However, one study reported increased mortality in PS in both males and females (SMR 2.1, 95% CI 1.2–3.6) [55].

Other seizure types

A significantly increased mortality was reported for myoclonic seizures (SMR 4.1), whereas no deaths were observed in patients with absence seizures with or without GTCS [51].

Table 2.7 Causes of death in epilepsy: proportionate mortality ratio (%).

Cause of death	Study		
	USA [51]	UK [52]	France [54][a]
Cerebrovascular	14	12	17
Heart disease	19	8	
Neoplasm, all	20	26	
Brain tumours	8	9	53
Pneumonia	8	14	
Suicide	1.6	0.5	
Accidents	6		
Seizure related	6	3	
SUDEP[b]		0.5	
Other	25	16	30

SUDEP, sudden unexpected death in epilepsy.

[a] Unprovoked seizures + progressive symptomatic.

Cause-specific mortality

Population-based studies with a control population

Population-based studies have found that persons with epilepsy have a significantly increased mortality due to cerebrovascular disease, SMR 2.6–4.2, neoplastic disorders, SMR 2.9–4.8 [51,52,55], and pneumonia, SMR 3.5–10.3 [51,52] (Table 2.7). The increased risk for death from neoplasm remained after exclusion of brain tumours [51,52]. An increased mortality due to accidents and non-heart/cerebrovascular circulatory disorders has also been reported [51]. Suicide is very uncommon in population-based studies of epilepsies [51,52,55].

Epilepsy and seizure-related mortality

Seizure-related death comprises death during SE, accidents and drowning caused by seizures and sudden unexpected death in epilepsy (SUDEP). Suicide in persons with epilepsy is sometimes categorized as epilepsy related.

The pathophysiological mechanisms in SUDEP are presently unknown but believed to be seizure related. Rates of SUDEP vary between different epilepsy populations, from 0.35 per 1000 person-years in an unselected population-based study [56], to around 1 per 1000 person-years in fairly unselected epilepsy populations [57–59], but are higher in more selected populations drawn from hospital series, and 10-fold the population rates annually in patients referred to epilepsy surgery or with continued seizures following surgery. In the only population-based study of SUDEP, 1.7% of all deaths in the epilepsy cohort and 8.6% of deaths in the 15–44 years group were due to SUDEP [56]. Between the ages of 20 and 40 years, SUDEP exceeded the expected rate of sudden death in the general population by nearly 24 times.

A study of childhood-onset epilepsy in Australia reported 22% of deaths to be seizure related [60], higher than other incidence cohorts, in which 0.9–5.5% of deaths were seizure related [51,52]. In prevalent epilepsy and mental retardation, seizure-related deaths are also rare, despite higher mortality noted generally in patients with frequent severe seizures. This may indicate that seizure frequency/severity in patients with neurodeficits in most

cases represent markers of the severity of the underlying aetiology that contribute to mortality, and less often are directly responsible for death.

Overall, it is reasonable to conclude that epilepsy doubles or triples mortality in people with epilepsy, mainly owing to the underlying causes of epilepsy and less often as a direct result of seizures. Thus, the potential to reduce mortality in epilepsy through reduction or elimination of seizures may be limited in the general epilepsy population but substantial in adolescents and younger adults with intractable epilepsy in whom SUDEP most often occurs [56].

There is no ready explanation for the late rise in mortality found in the Rochester, Minnesota, study 25–29 years after onset of epilepsy [51]. It may be seizure related, due to underlying diseases, due to late effects of antiepileptic treatment, or due to a combination of these and other factors. The increased mortality observed during the first 5 years following remission of seizures also indicates the contribution of non-seizure-related factors to mortality in epilepsy [51].

Mortality trends over time

During the last century a major improvement in the standard of living and availability of medical care has taken place. Although one would anticipate that this has decreased mortality in epilepsy, it is difficult to know for certain because of the lack of reliable data on epilepsy mortality over time. Studies evaluating trends in epilepsy mortality are based on death certificates, causing the methodological problems discussed above.

The annual mortality rates for epilepsy declined from the 1950s to the 1970s [61]. A study of epilepsy mortality in the UK and the USA for 1959–94 found similar secular trends for both countries and for both sexes [62]. Epilepsy mortality declined profoundly after 1950 among people younger than age 20 years. A less marked decline was found in adults while mortality in the elderly declined between 1959 and 1974 but then increased. A marked birth cohort effect was found, with a fall with each successive birth cohort indicating that aetiological risk factors varied by generation [62]. The birth cohort effect could be due to a decrease in incidence in epilepsy which, as mentioned earlier, has been found for childhood epilepsy. The increase in mortality during the last decades in the elderly with epilepsy could be an effect of the high incidence of epilepsy in the elderly, which almost doubled during a 50-year interval (see section on epidemiological time trends).

Life expectancy

The higher mortality rates in people with epilepsy are reflected in reduced life expectancies. In the UK, life expectancy was found to be reduced by up to 2 years for people with idiopathic/cryptogenic epilepsy, and by up to 10 years in people with symptomatic epilepsy [63]. Reductions were highest at the time of diagnosis and diminished with time.

Prognosis in largely untreated populations

If epilepsy were a truly chronic condition without increased mortality or remission, the prevalence rate of active epilepsy would be similar to the cumulative incidence rate, but in fact it is much lower. To what extent can this discrepancy be explained by increased mortality and by seizure remission? It is known that mortality is increased in epilepsy, both in more and in less developed countries. The relative mortality may be similar in developed and developing countries, reflecting a two- to threefold increase. However, the highest mortality of general populations is found in less developed countries, and multiplying that mortality two to three times means that the annual mortality is much higher in epilepsy populations of less developed countries than in epilepsy populations elsewhere. A large proportion, probably the majority, of untreated people with epilepsy anywhere in the world are no longer counted as having epilepsy not because of death but because seizures remit spontaneously. Studies of largely untreated populations with longstanding epilepsy in developing countries indicate that the duration of epilepsy before treatment does not seem to affect the likelihood of remission [64].

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3 Aetiology of Epilepsy

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Epilepsy is often multifactorial [1]. Even in the presence of a major aetiology, other factors (genetic and environmental) can play a part in its clinical manifestations. Lennox recognized this in 1960 [2] with his picturesque analogy of *the river* (Fig. 3.1). He also used the analogy of a reservoir in which the

> Causes may be represented as the sources of a reservoir. At the bottom is the already present volume of water, which represents the person's predisposition, a fundamental cause. But the reservoir is supplied also by streams which represent the contributory conditions, such as lesions of the brain acquired since conception, certain disorders of bodily function and emotional disturbances.

It is usual to differentiate the aetiology of epilepsy from factors that contribute to seizure precipitation in patients who already present with the propensity to epilepsy. Here, this convention will be maintained, albeit recognizing that this is a relative not absolute distinction.

The range of aetiology varies in different age groups, patient groups, and geographic locations. Broadly speaking, congenital and perinatal conditions are the most common causes of early childhood-onset epilepsy, whereas in adult life epilepsy is more likely to be a result of external non-genetic causes, but this distinction is by no means absolute. In late adult life, vascular disease is increasingly common. In certain parts of the world, endemic infections are common causes – including tuberculosis (TB), cysticercosis, human immunodeficiency virus (HIV) and viral diseases. The specific 'epilepsy syndromes' are also highly age dependent. The approximate frequencies of different aetiologies in a typical Western population are shown in Table 3.1.

Epilepsy as a result of genetic or developmental causes

Heredity plays a very important role in the production of epilepsy, but mechanisms are complex. Gene expression can be variable and influenced by environmental factors, and the epilepsies are often also age dependent. Single-gene disorders probably underlie only 1–2% of all epilepsies, and usually in these conditions there are additional neurological or systemic features. It is useful to consider the 'pure' epilepsies separately from the epilepsies associated with other neurological defects, although this distinction, like most in medicine, is somewhat artificial and transitional cases occur in a grey area between categories. Epilepsies as a result of some developmental anomalies have genetic and acquired forms but are included here for the sake of convenience.

Pure epilepsies as a result of single-gene disorders

Pure epilepsies resulting from single-gene disorders are generally rare conditions, described in families (sometimes single families), but are potentially important for the mechanistic light they may throw on the more common polygenic epilepsies. Interestingly, almost all of the genes identified that contribute to susceptibility to epilepsy are genes that code for ion channels [3] (Table 3.2) [3,4]. In this sense, epilepsy has been recognized in recent years to be one of a burgeoning group of neurological disorders with intermittent symptoms, which have underlying ion channel genetic defects.

Benign familial neonatal convulsions

The syndrome of benign familial neonatal convulsions is a condition that is inherited in an autosomal dominant fashion and is due to mutations of voltage-gated potassium channel genes *KCNQ2* and *KCNQ3* [5]. The abnormalities of these genes result in reduced potassium conductance and hence enhanced neuronal excitability. Why the effects are restricted to the first few weeks of life is unclear. One plausible hypothesis is that the mutated channels are replaced by other potassium channels that are up-regulated early in life.

Autosomal dominant nocturnal frontal lobe epilepsy

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was the first 'pure epilepsy' in which the causal gene was found [6,7]. Various mutations in the α_4- and β_2-subunits of the nicotinic acetylcholine receptor have been identified in families with this interesting condition. There is often a strong family history and, when investigated, even apparently unaffected members in a family can have subtle nocturnal events, mistaken as simply restlessness or normal sleep phenomena.

Generalized epilepsy with febrile seizures

Generalized epilepsy with febrile seizures plus (GEFS+) is a heterogeneous form of epilepsy inherited in an autosomal dominant fashion, with age-specific manifestations and variable penetrance (penetrance of about 60% was found in the original families) [8,9]. Many different mutations have been described in either the α- or β-subunits of the voltage-gated sodium channel genes *SCNIA* and *SCNIB*, and more recently the γ2-subunit of the $GABA_A$ receptor *GABRG2* gene in families from many places in the world. Functional studies have confirmed that these mutations confer abnormal membrane excitability.

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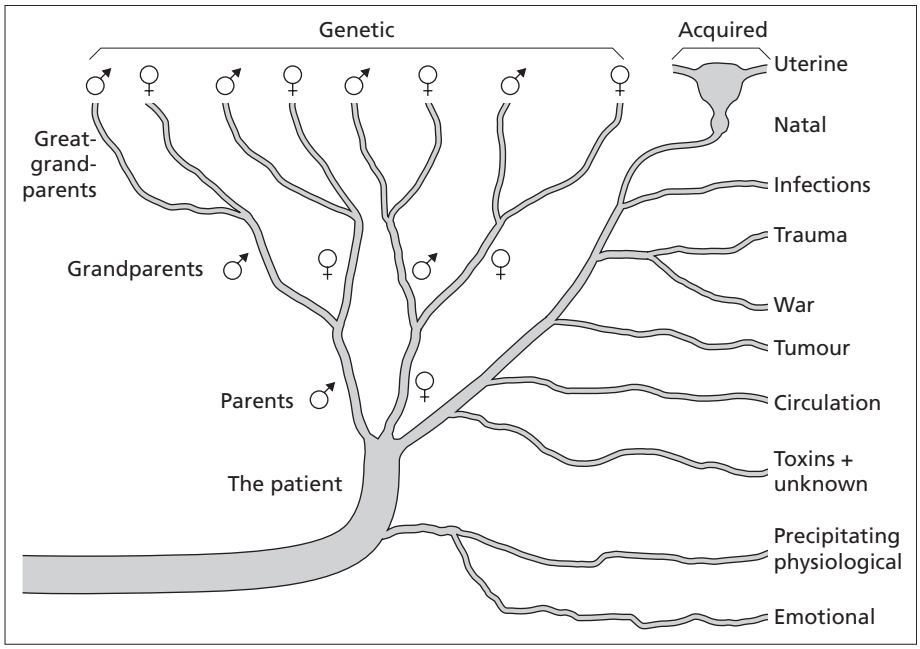

Fig. 3.1 The multifactorial nature of epilepsy was illustrated by Lennox as the analogy of a river in which many different streams (causes) contribute to the occurrence of a seizure.

Table 3.1 Approximate frequency of different causes of epilepsy in a general Western population.

Cause	Approximate frequency (%)
Idiopathic (probably oligogenic)	10–30
Vascular	10–20
Congenital	5–10
Neurodegenerative/other neurological disorder	5–10
Hippocampal sclerosis	5–10
Brain tumour	5–10
Trauma	5
Childhood epilepsy syndrome	5
Infectious metabolic, toxic causes	5
Single-gene disorder	1–2
Unknown cause (cryptogenic epilepsy)	30

Dravet's syndrome

Dravet's syndrome [severe myoclonic epilepsy of infancy (SMEI)] is a severe form of epilepsy in which many (but not all) patients have mutations in the *SCNIA* gene, the same gene that causes the more benign GEFS+, and indeed there are families in which both phenotypes coexist [10]. Furthermore, despite the frequency of a family history, curiously, the mutations are in the vast majority of cases *de novo*.

Other single-gene 'pure epilepsy' syndromes

A rag-bag of other single-gene epilepsy syndromes have been described, in either single or a few families, and include [11]: familial adult myoclonic epilepsy (in a few families from Japan), familial autosomal recessive idiopathic myoclonic epilepsy of infancy (in an Italian family), X-linked infantile spasms, benign familial infantile convulsions, familial partial epilepsy with variable foci (linked to 22q), autosomal dominant epilepsy with auditory features (linked to 10q), familial temporal lobe epilepsies, and autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp. Autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD) is a rare condition with an unknown genetic basis but which exhibits anticipation, suggesting that it may be a triplet repeat syndrome.

Pure epilepsies with complex (presumed polygenic) inheritance

Pure epilepsies with complex inheritance are far more common than the single-gene epilepsies. Categories of idiopathic and cryptogenic epilepsy, both focal and generalized, exist with a strong presumption of a polygenic genetic basis (i.e. with complex inheritance, which does not follow simple mendelian rules). These conditions are divided into the idiopathic generalized epilepsies (IGE) and the benign partial epilepsies of childhood, and have been the subject of intensive genetic study, but to date no common susceptibility genes have been identified [12].

The extent to which other cryptogenic epilepsies have a genetic basis is less clear (e.g. febrile convulsions, cryptogenic West syndrome and cryptogenic Lennox–Gastaut syndrome). The conditions are probably best conceptualized as polygenic disorders in which the phenotype is the result of interactions between susceptibility genes and environmental effects. There is often no strong family history, and genetic studies have to be conducted using case–control methodology in large populations. The phenotypes are wide, and the susceptibility genes may also have a widely varying polymorphism. In this context, the concept of epilepsy syndromes as discrete entities that are clinically homogeneous and biologically distinct cannot be sensibly sustained. More attractive is the concept of the neurobiological continuum, in which there are widely varying phenotypes with similar genetic defects and also overlapping phenotypes caused by differing gene abnormalities. To confuse the picture further, many of these phenotypes can result from a range of identifiable acquired and congenital brain disorders (symptomatic cases). In this sense, the epilepsy

Table 3.2 Single genes found to be the cause of pure epilepsy.

Human epilepsy	Affected gene	Affected current	Effect on the current	Main functional mechanism
BFNC	*KCNQ2, KCNQ3*	M-current	Loss of function	Decreased expression or modifications of gating kinetics that reduce K^+ M-current induced hyperpolarization
Focal familial seizures and myokymia	*KCNA1*	Delayed rectifier	Loss of function	Decreased delayed rectifier K^+ current by various mechanisms
Generalized epilepsy and paroxysmal dyskinesia	*KCNMA1*	I_{KCa}, (BK)	Gain of function	Enhanced Ca^{2+} sensitivity (cell hyperexcitability may be caused by rapid action potential repolarization and enhanced recurrent firing)
BFNIC	*SCN2A*	I_{Na}	Gain of function	Increase of current by various modifications of voltage dependence of gating
GEFS+ type 1	*SCN1B*	I_{Na}	Gain of function	Variable according to the expression system, often loss of modulation of I_{NaT} inactivation
GEFS+ type 2	*SCN1A*	I_{Na}	Gain or loss of function	Variable according to the mutation, expression system, and complementary DNA used Slowed time course of I_{NaT} inactivation and faster recovery from inactivation Decreased use-dependent inactivation Enhanced I_{NaP} fraction and decreased fast inactivation of I_{NaT} Hyperpolarizing shift of both I_{NaT} activation and inactivation causing a hyperpolarizing shift of window current Reduced current and enhanced recovery from slow I_{NaT} inactivation Depolarizing shift of I_{NaT} steady-state inactivation because of altered interaction with β1 subunit
SMEI	*SCN1A*	I_{Na}	Gain or less of function	No current Enhanced I_{NaP} fraction
ICEGTC	*SCN1A*	I_{Na}	Gain or loss of function	No current Various effects on gating properties according to the mutation
FS	*SCN1A*	I_{Na}	Loss of function	Decreased current, pocitive shift voltage dependence of activation
Absence epilepsy and episodic ataxia	*CACNA1A*	I_{Ca} (P/Q)	Loss of function	Decreased P/Q Ca^{2+} current by reduced membrane targeting
CAE	*CACNA1H*	I_{Ca} (T)	Gain or loss of function	Various effects on gating properties of T-type Ca^{2+} channels
IGE and episodic ataxia	*CACNB4*	I_{Ca}	Gain of function	Decrease in the fast inactivation time constant when co-expressed with α subunit
IGE with absences and convulsions	*CLCN2*	I_{Cl}	Loss of function	Complete loss of function causing decreased transmenbrane Cl gradient (and GABA inhibition) Changes in voltage-dependent gating (membrane depolarization?)
GEFS+ type 3	*GABRG2*	I_{GABA}	Loss of function	Decreased current amplitude by reduced membrane targeting and receptor assembly
CAE and FS	*GABRG2*	I_{GABA}	Loss of function	Loss of benzodiazepine sensitivity
JME	*GABRA1*	I_{GABA}	Loss of function	Reduced GABA sensitivity and altered channel gating
ADNFLE type 1	*CHRNA4*	nAChR	Loss of function	Various effects
ADNFLE type 3	*CHRNB2*	nAChR	Gain of function	Slower desensitization Increase in acerylcholine sensitivity

BFNC, benign familial neonatal convulsions; BFNIC, benign familial neonatal–infantile convulsions; I_{Na}, sodium current; GEFS+, generalized epilepsy with febrile seizure plus; I_{NaT}, transient sodium current; I_{NaP}, persistent sodium current; SMEI, severe myoclonic epilepsy in infancy; ICEGTC, intractable childhood epilepsy with generalized tonic–clonic seizures (a disorder similar to SMEI); FS, febrile seizures; CAE, childhood absence epilepsy; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; nAChR, nicotinic acetylcholine receptor.

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syndrome can be thought of as a genetically determined end-point response of dysfunctional brain tissue to an acquired insult.

Epilepsies in other single-gene disorders

At least 240 single-gene and chromosomal disorders result in neurological disorders in which epilepsy is part of the phenotype. Most are rare or very rare, manifest initially in childhood and present for diagnosis to paediatric neurological services rather than to an epilepsy specialist. In only a few of these conditions does epilepsy have distinctive features or is a predominant or consistent feature: exceptions are the progressive myoclonus epilepsies and some neurocutaneous syndromes. Conditions associated with epilepsy are shown in Table 3.3.

Table 3.3 Risk for epilepsy in genetic disorders.

Category	No increase in risk	Slight increase in risk (5–20%)	High risk (>20%)
Chromosome disorders	Cri-du-chat syndrome Sex chromosome disorders	Trisomy 21 syndrome Other chromosome anomalies	Fragile X syndrome Trisomy 13 syndrome Trisomy 18 syndrome Wolf–Hirschhorn syndrome
Contiguous gene disorders		Prader–Willi syndrome	Angelman's syndrome Miller–Dieker syndrome
Metabolic disorders	Endocrine disorders Exocrine disorders Glycogen storage disease Mucopolysaccharidoses	Acute intermittent porphyria Leukodystrophies	Amino acid disorders Glycogen storage disorders Homocystinuria Krabbe's disease Leigh's syndrome Menkes' disease Mitochondrial disorders Organic acidurias Peroxisomal disorders Pyridoxine-dependent seizures
Genetic syndromes			
Short stature	Bloom's syndrome Cockayne's syndrome Dubowitz's syndrome Hallermann–Streiff syndrome Noonan's syndrome	Brachmann–de Lange syndrome Robinow's syndrome Rubinstein–Taybi syndrome Smith–Lemli–Opitz syndrome Xeroderma pigmentosum (de Sanctis–Cacchione variant)	
Early overgrowth	Marshall–Smith syndrome Smith–Golabi–Behmel syndrome Sotos' syndrome Weaver's syndrome	Bannayan–Riley–Ruvalcaba syndrome Beckwith–Wiedemann syndrome Cohen's syndrome	Borjeson–Forssman–Lehmann syndrome
Skeletal dysplasias	Achondroplasia Apert's syndrome Metaphyseal dysplasias Osteochondrodysplasias Osteopetrosis Saethre–Chotzen syndrome	Albright's osteodystrophy Crouzon's syndrome Hypophosphatasia Pfeiffer's syndrome	Christian's syndrome
Facial defects	Moebius sequence Oculo-auriculo-vertebral syndromes Treacher Collins syndrome Other branchial arch syndromes	FG syndrome Langer–Giedion syndrome Progressive hemifacial atrophy	Acrocallosal syndrome Cardiofaciocutaneous syndrome Coffin–Lowry syndrome
Connective tissue disorders	All except homocystinuria		
Neurocutaneous disorders	Neurofibromatosis-2	Neurofibromatosis-1	Encephalocraniocutaneous lipomatosis Epidermal naevus Hemimegalencephaly Incontinentia pigmenti Sturge–Weber syndrome Tuberous sclerosis
Ectodermal/mesodermal dysplasias	All disorders		
Disorders of brain development	Posterior fossa disorders		Agenesis of corpus callosum syndromes Holoprosencephaly Lissencephaly Other disorders of neuroproliferation, migration and connectivity
Neurodegenerative disorders	Ataxias Parkinson's disease and variants	Alzheimer's disease Hallervorden–Spatz disease Wilson's disease	Ceroid lipofuscinosis Dentato-rubro-pallido-luysian atrophy (myoclonus epilepsy form) Juvenile-onset Huntington's disease Neuroacanthocytosis Rett's syndrome

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The *inborn errors of metabolism* are conditions in which biochemical defects are inherited, usually in an autosomal recessive fashion, and in which the epilepsy is one symptom within a much broader spectrum of learning disability, neurological and systemic features [13]. These include conditions with intermittent or persistent metabolic changes, including hypoglycaemia, hyperammonaemia, hypocalcaemia, hyperglycinaemia, metabolic acidosis, ketoacidosis, abnormal amino acid or oligosaccharide profile, mucopolysaccharidoses and lipid storage diseases. Epilepsy is particularly found in Angelman's syndrome [14], Tay–Sachs disease, Niemann–Pick disease type C, Krabbe's disease, amino acid disorders and glycogen storage disorders. In a substantial number of cases presenting with epilepsy and learning disability, on a congenital basis, no cause can be identified. Porphyria is another important cause with geographical variation [15].

Progressive myoclonic epilepsy (PME)

Progressive myoclonic epilepsy (PME) has a rather specific phenotype, which can be caused by a variety of genetically determined neurological disorders (Table 3.4). In most parts of the world, there are six leading underlying conditions: mitochondrial disorders, Unverricht–Lundborg disease, dentato-rubro-pallido-luysian atrophy (DRPLA), Lafora body disease, neuronal ceroid lipofuscinosis (NCL) and sialidosis.

Baltic myoclonus (Unverricht–Lundborg disease)

Baltic myoclonus is the most benign form of progressive myoclonic epilepsy. It is an autosomal recessive disorder due to mutations in the *EPM1* gene coding for the cystatin B protein, a protease inhibitor. The most common mutation is an unstable expansion of a dodecamer repeat. Diagnosis can be made by genetic testing [16,17].

Table 3.4 Causes of progressive myoclonic epilepsy (PME).

Most common causes
Baltic myoclonus (Unverricht–Lundborg disease)
Ceroid lipofuscinoses
Dentato-rubro-pallido-luysian atrophy (DRPLA)
Lafora body disease
MERRF, mitochondrial disease
Sialidoses
Rarer causes
Alpers' disease
Alzheimer's disease
Biotin-responsive progressive myoclonus
Coeliac disease
Gaucher's disease
GM2 gangliosidosis (juvenile type)
Hexosaminidase deficiency
Huntington's disease
Juvenile neuroaxonal dystrophy
Menkes' disease
Non-ketotic hyperglycinaemia
Phenylketonuria
Tetrahydrobiopterin deficiencies
(In some patients, no cause can be identified)

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Dentato-rubro-pallido-luysian atrophy

Dentato-rubro-pallido-luysian atrophy is inherited in an autosomal dominant fashion. It occurs with markedly varying frequency around the world, being particularly common in Japan (a frequency of 0.2–0.7 per 100 000 persons) and in northern Europe. It is a triplet repeat disorder involving the *DRPLA* gene which is of uncertain function. The normal repeat number is between 6 and 35 and the condition is present with full penetrance when the repeat number is greater than 48. The diagnosis of DRPLA rests on positive family history, the characteristic clinical findings, and the detection of an expansion of a CAG/polyglutamine tract in the *DRPLA* gene. The CAG repeat length in individuals with DRPLA ranges from 48 to 93 base units. Molecular genetic testing is widely available. Diffuse high-intensity areas deep in the white matter are often observed on T2-weighted MRI in individuals with adult-onset DRPLA of long duration.

Lafora body disease

Lafora body disease, an autosomal recessive condition mostly reported from southern Europe, is characterized by the presence of Lafora bodies, which are periodic acid–Schiff (PAS)-positive intracellular polyglucosan inclusions found in neurones, sweat glands and a variety of other sites. A mutation in the *EPM2A* gene on chromosome 6q24, which codes for a putative protein tyrosine phosphatase gene, is sometimes responsible. Fourteen different mutations in 24 families are now known. The diagnosis can be confirmed by histological examination of skin (which should include eccrine glands), liver or muscle biopsy material, but genetic testing has now rendered this largely unnecessary [18].

Mitochondrial cytopathy

Mitochondrial cytopathy [myoclonic epilepsy with ragged red fibres (MERRF)] is caused by a range of point mutations or deletions of mitochondrial DNA, or nuclear genes linked to mitochondrial function, which result in dysfunction of the mitochondrial respiratory chain [19–21]. On the inner mitochondrial membrane there are over 70 different polypeptides that form the respiratory chain and 13 of these polypeptides are encoded by mitochondrial DNA; defects have been described in all of these. Two classic phenotypes [MERFF and mitochondrial encephalopathy with lactic acidaemia and stroke (MELAS)] occur, in which seizures are a common and important symptom, although intermediate and transitional cases are not uncommon. In a third mitochondrial disorder, the Leigh syndrome and neuropathy, ataxia and retinitis pigmentosa (NARP) continuum, seizures are also common but not a predominant feature. Alpers' disease has now been found to be due to a mitochondrial defect, inherited by nuclear DNA mutations. The diagnosis of MERRF is made by the findings of ragged red fibres on muscle biopsy in 80% of cases, and biochemical analysis will show decreased activity in respiratory chain enzymes. MRI may show atrophy, T2 signal change and also basal ganglia calcification. In 90% of cases, the genetic defect is an A→G transition at nucleotide 8344 in the $tRNA^{lys}$ gene of mtDNA, and some other cases are caused by *T8356C* or *G8363A* mutations. Genetic testing is available. Heteroplasmy is responsible for some of the phenotypic variation and can complicate genetic diagnosis.

Neuronal ceroid lipofuscinosis

The NCLs are a group of inherited lysosomal storage disorders that may present with progressive myoclonic epilepsy, and mental and motor deterioration [22]. These are the commonest of the hereditary progressive neurodegenerative diseases, occurring generally in about 1:25 000 live births, but with marked geographic variation with a particularly high frequency in Finland. The phenotypes are categorized by age of onset: infantile neuronal ceroid lipofuscinosis (INCL), late-infantile (LINCL), juvenile (JNCL), adult (ANCL) and northern epilepsy (NE). Myoclonic epilepsy is a feature of all types. Almost all cases are inherited in an autosomal recessive manner although an autosomal dominant form of adult-onset NCL has been described. Carriers show no symptoms. The diagnosis of a NCL is based on clinical findings, electron microscopy of biopsied tissues, and, in some instances, assay of enzyme activity or enzyme levels, and molecular genetic testing. Causative mutations in a variety of genes (NCL and MFSD8 genes) have been identified, which vary geographically. MRI shows atrophy and sometimes T2 hyperintensity, and visually evoked responses (VEPs) and electroretinogram (ERG) responses are abnormal. White cells are vacuolated. Electron microscopy of white blood cells, skin, conjunctiva, or other tissues typically reveals lysosomal storage material manifest as fingerprint, curvilinear profiles, or granular osmophilic deposits. The levels of enzyme products of each of the six genes can also be assayed. There are six causative genes – *PPT1*, *CLN2*, *CLN3*, *CLN5*, *CLN6* and *CLN8* – and over 140 mutations described. There is a marked geographic variation in the genetic abnormalities, with *CLN8* abnormalities for instance found only in Finland. Genetic testing, and also prenatal testing, for each is available.

Sialidosis

Sialidosis is less common than the other causes of progressive myoclonic epilepsy. There are at least two variants [23]. All cases are inherited in an autosomal recessive manner. Type 1 sialidosis (cherry-red spot myoclonus syndrome) is due to *N*-acetyl neuraminidase deficiency: a gene has been mapped to chromosome 6p21.3. In Type 2 sialidosis (also known as galactosidase), there are defects in β-galactosidase activity in addition to those in *N*-acetyl neuraminidase. One gene has been mapped to chromosome 20. The genetic basis of this disorder is complex and not completely elucidated, and involves both the gene for Neu-1 and the gene for cathepsin A, which forms a complex with Neu-1. Diagnosis is confirmed by finding elevated urinary sialyloligosaccharides and by assaying enzyme activity in leucocytes and cultured skin fibroblasts.

Epilepsies in neurocutaneous syndromes

The so-called neurocutaneous conditions often result in epilepsy [24,25]. Tuberous sclerosis complex, Sturge–Weber syndrome and neurofibromatosis (type 1) are the most important, and are not uncommonly encountered in epilepsy clinics. Other rare conditions causing epilepsy include hypomelanosis of Ito, epidermal naevus syndrome, hereditary haemorrhagic telangiectasia, midline linear naevus syndrome, incontinentia pigmenti and Klippel–Trenaunay–Weber syndrome.

Tuberous sclerosis

Tuberous sclerosis (synonym: tuberous sclerosis complex, TSC) is a common and important cause of epilepsy [26,27]. The incidence may be as high as 1:5800 live births and there is a high spontaneous mutation rate (1:25 000). It is inherited in an autosomal dominant fashion and is usually caused by mutations of the *TSC1 or TSC2* genes: both are tumour suppressor genes. There is no obvious phenotypic difference between individuals with mutations in either gene. To date, about 300 unique *TSC1* or *TSC2* mutations have been identified in nearly 400 separate patients/families. The mutations are primarily small deletions, insertions or nonsense mutations; in contrast, *TSC2* mutations also include significant numbers of missense mutations, large deletions and rearrangements. Between 60% and 80% of patients with TSC enrolled in research studies have an identifiable *TSC1* or *TSC2* mutation. The condition is a form of cortical dysplasia, and the histological appearances of the tumours show similar features to other forms of focal cortical dysplasia. There is considerable clinical variability in the manifestations of tuberous sclerosis, and the extent to which some other forms of cortical dysplasia represent *form fruste* cases will no doubt be established by modern genetic studies. Molecular genetic testing for diagnostic confirmation and prenatal testing of the *TSC1* and *TSC2* genes is available but complicated by the large size of the two genes, the large number of disease-causing mutations and the high rate of somatic mosaicism (10–25%).

Neurofibromatosis (type 1)

Neurofibromatosis type 1 (NF1) is a common dominantly inherited genetic disorder, occurring in about 1:3000 live births. Almost one-half of all cases are new mutations. The mutation rate for the *NF1* gene is about 1:10 000, among the highest known for any human gene. It is a large gene, and many different mutations have resulted in the clinical manifestations. Although the penetrance is essentially complete, the clinical manifestations are extremely variable. In NF1, the incidence of epilepsy is about 5–10% [28]. Genetic counselling and testing is available but it is complex and needs to be carried out by those who have experience of the condition.

Sturge–Weber syndrome

Sturge–Weber syndrome is an uncommon sporadic developmental disorder of uncertain causation. The principal clinical features are a unilateral or bilateral port wine naevus, epilepsy, hemiparesis, mental impairment and ocular signs. This is a highly characteristic clinical constellation, and diagnosis is clinically based. Severe seizures in this condition result in neurological deterioration and are an argument for early surgical intervention [29]. Diagnosis is made on clinical and radiological grounds.

Epilepsies in disorders of chromosome structure

Epilepsy is also a feature of two common chromosomal abnormalities: Down syndrome and fragile X syndrome [30]. It also takes a highly characteristic form in the rare ring chromosome 20. Other uncommon chromosomal abnormalities in which epilepsy is found include trisomy 12p, 8, 13; ring chromosome 14; partial monosomy 4p (Wolf–Hirschhorn syndrome); inverted duplication of pericentromeric chromosome 15; and Klinefelter's

syndrome (where epilepsy occurs in about 10% of cases). In all these conditions, there are additional behavioural and intellectual disabilities and characteristic dysmorphic features. The seizures often take multiple forms, including myoclonus, and are of variable severity. Genetic testing is available for most conditions.

Down syndrome

The Down phenotype occurs in about 1:650 live births. It is usually caused by trisomy of chromosome 21, and triplication of 21q22.3 results in the typical phenotype. In 95% of cases, the cause is a non-disjunction, and in about 4% an unbalanced translocation. About 1% of cases are mosaics. The risk of trisomy increases with maternal age. Epilepsy is present in up to 12% of cases and electroencephalogram (EEG) abnormalities in more than 20% [31]. Genetic testing and prenatal screening are available.

Fragile X syndrome

Fragile X syndrome is a condition due to increased number of CGG codon repeats (typically >200) in the *FMR1* gene (at Xq27.3) accompanied by aberrant methylation of the gene. It is an X-linked condition in which the presenting symptom is usually mental retardation, which is moderate in affected males and mild in affected females. Epilepsy is a common feature. Fragile X syndrome occurs in about 1:4000 male births and is the most commonly identified cause of mental retardation. The carrier rate in unaffected females with the permutation (CGG codon repeats of <200) may be as high as 1:250, with some geographic and racial variation. Repeat numbers vary, and mosaicism is common, and these may account for the variable clinical features. Genetic and prenatal testing are widely available. The methylation status of the gene can also be identified using Southern blot. Identification of the abnormal protein is not usually required.

Ring chromosome 20

Ring chromosome 20 is a rare condition but one in which epilepsy is the predominant feature and has a highly characteristic phenotype [32]. The locus of fusion between the deleted short and long arms of the chromosome is at p13q13, p13q13.3.3 or p13q13.33. This is a sporadic condition, and can be identified by genetic testing. Mosaicism is common and at least 100 mitoses may need to be examined before excluding the condition.

Epilepsies as a result of developmental anomalies of cerebral structure (the 'cortical dysplasias')

Cortical dysplasia (synonyms: cortical dysgenesis, malformations of cortical development) is a term that is applied to developmental disorders of the cortex producing structural change. A minority of these conditions are caused by identifiable genetic abnormalities. Others are caused by environmental influences such as infection, trauma, hypoxia or exposure to drugs or toxins. In most cases the cause is unclear. The form of dysplasia consequent on environmental insults depends not only on the nature of the insult, but also on the stage of development at which it occurred. Cortical malformations can be due to abnormal neuronal and glial proliferation, abnormal neuronal migration or abnormal synaptogenesis, cortical organization or programmed cell death [33–35].

The true prevalence of these conditions, previously thought to be rare, has only become apparent with the widespread use of MRI, which can detect cortical dysplasia in cases previously classified as cryptogenic epilepsy. Epilepsy is a leading feature of these conditions, usually, but not always, in association with learning disability and other neurological findings.

Hemimegalencephaly

Hemimegalencephaly describes a gross structural abnormality which can be the end result of various cerebral processes and insults [36]. One cerebral hemisphere is enlarged and is structurally abnormal with thickened cortex, reduced sulcation and poor or absent laminar organization. Giant neurones are found throughout the brain and in 50% of cases balloon cells are found. The condition can occur in isolation, associated with other cortical dysplasias or as part of other syndromes (notably tuberous sclerosis or other rarer neurocutaneous syndromes, such as epidermal naevus syndrome, Klippel–Trenaunay–Weber syndrome, neurofibromatosis type 1 or hypomelanosis of Ito). The restriction of the abnormality to one hemisphere may be a result of somatic mosaicism, and it has been suggested that the condition is due to defects in the process of programmed cell death (apoptosis) in early fetal life.

Focal cortical dysplasia

Focal cortical dysplasia is a common form of dysplasia, important to identify because of its potential for surgical therapy [37,38]. The term encompasses a variety of subtypes with different histological appearances, possibly a result of formation at different stages of embryogenesis. In some, the cortical lamination is normal, but in others there may be associated macrogyria and polymicrogyria. Focal dysplasia can occur in any part of the cortex, and varies greatly in size. There are often widespread minor dysplastic abnormalities, associated with some forms of focal cortical dysplasia, although in the Taylor form, diagnosed by the histological presence of 'balloon cells', the dysplastic changes are more limited.

Schizencephaly

Schizencephaly refers to the presence of clefts in the cortex, stretching from the surface to the ventricle [39]. The clefts are subdivided into open-lip schizencephaly (in which the walls of the cleft are separated) and closed-lip schizencephaly (in which the walls of the cleft are not separated). The clefts can be unilateral or bilateral and they are usually perisylvian in location. Schizencephaly is often associated with polymicrogyria and less often with other focal cortical dysplastic anomalies, corpus callosum agenesis or septo-optic dysplasias. The cortex may or may not have normal lamination. The pathogenesis in some cases is a failure of migration and in others an environmental insult causing focal necrosis of developing cortex. The causes are heterogeneous, and include germline mutations of the homeobox gene *EMX2* and environmental insults during development, including radiation, infection and ischaemia.

Agyria–pachygyria band spectrum

Lissencephaly, pachygyria, agyria and subcortical band heterotopia are descriptive terms denoting abnormalities of cortical gyration, and are grouped together as they show an interconnected genetic basis: in all of these, the gyration is simplified and the cortex is thickened. Lissencephaly (literally meaning smooth

brain) is the most severe form, in which gyration is grossly diminished or even absent. Subcortical band heterotopia (synonym: subcortical laminar heterotopia, band heterotopia, double cortex syndrome) denotes the presence of a band of grey matter sandwiched by white matter below the cortical grey matter. The band may be thin or thick and can merge with overlying cortex, in which case the cortex takes a macrogyric form. When the bands are thin and clearly separated from the cortical ribbon, the ribbon itself may appear normal. Thicker bands are usually associated with macrogyria. *Macrogyria* refers to thickened cortex and can occur as an isolated phenomenon. It is variable in extent and, when focal, it is indistinguishable on clinical or imaging grounds from some forms of focal cortical dysplasia.

Most forms of lissencephaly occur without other non-cerebral malformations [isolated lissencephaly sequence (ILIS)] [40]. Isolated lissencephaly is present in 12 of one million live births. Sixty to eighty per cent of cases of isolated lissencephaly are caused by identifiable mutations in *LIS1*, on 17p13.3, or in X-linked dominant lissencephaly (XLIS) (in *DCX*) on Xq22.3–q24: in 40% the entire gene is deleted. *LIS1* lissencephaly is predominantly posterior in location, and the condition occurs in both sexes and is sporadic. Conversely, XLIS cases occur almost always in boys and the brain anomaly tends to be anterior in location. Genetic testing is available for both forms.

Other forms of lissencephaly have more widespread associations. The best known is *Miller–Dieker syndrome*, which is caused by large deletions of *LIS1* and of several other contiguous genes on 17p13.3. Genetic testing is available.

Subcortical band heterotopia is caused in about 80% of cases by germline deletions in the *DCX* (XLIS) gene and occurs almost always (but not exclusively) in females. The pachygyria and bands are anteriorly predominant. The genetic anomaly in the other 20% of cases has not been identified. The rare cases of *subcortical band heterotopia* in boys are probably caused by missense mutations in *DCX* or *LIS1*.

Agenesis of the corpus callosum

Agenesis of the corpus callosum is a dysplastic anomaly that occurs in various genetic and congenital disorders. Epilepsy is an invariable association, and often a leading symptom. In *Aicardi's syndrome*, the corpus callosum agenesis is associated with periventricular heterotopia, thin unlayered cortex and diffuse polymicrogyria. It is observed only in females (the only exception being males with two X chromosomes) and is X-linked with male lethality. The causal gene has not yet been identified but linkage to Xp22.3 has been reported. The syndrome may be due to skewed X chromosome inactivation. Other syndromes with agenesis of the corpus callosum exist, and this anomaly may co-exist with other dysplastic features. The *L1 syndrome* is associated with mutations in the *L1CAM* gene and presents as hydrocephalus, mental retardation, spasticity and epilepsy.

Polymicrogyria

The appearance of small and prominent gyri, separated by shallow sulci, is known as polymicrogyria. It can be diffuse or localized, and varies in severity as well as extent. The underlying cortex is invariably thickened, and can be unlayered or show an abnormal four-layered structure. The former may be a migrational defect in weeks 13–18 of fetal life, and the latter the result of ischaemia or perfusion failure between weeks 12 and 24 of fetal life. Epilepsy is the leading clinical feature, associated with learning disability and focal neurological signs. No gene is yet discovered, but linkage has been reported to X28p in 22q11.2m and in other cases due to 22q11 deletion and mutations of the *AHI1* gene.

Periventricular nodular heterotopia

The presence of subependymal nodules of grey matter, located along the supralateral walls of the lateral ventricles, is known as periventricular nodular heterotopia [synonyms: bilateral periventricular nodular heterotopia (BPNH), subependymal nodular heterotopia (SENH)]. The heterotopia is usually bilateral, although not always. It is much more common in females and conforms to X-linked dominant transmission, and is probably the most common of all the cortical dysplasias. Almost all cases have shown mutations in the *FLN1* (filamin-1) gene [41,42].

Other dysplasias

Various other types of dysplastic lesion exist, including sheets of abnormal neurones forming linear streaks in the white matter, abnormal cortical patterning (including stellate-like gyral formations), isolated clusters of grey matter within white matter and microdysgenesis. The last term refers to abnormally placed microscopic clusters of heterotopic neurones often associated with abnormal lamination of the cortex. Normal brains have occasional heterotopic cells, and distinguishing the truly pathological from the normal is, to an extent, a subjective judgement. Because of this, widely varying estimates of the frequency of microdysgenesis have been made. At one extreme is a study showing microdysgenesis in 38% of postmortem specimens in epilepsy compared with a frequency of only 6% in control subjects.

Epilepsy as a result of an acquired disorder

Epilepsy resulting from an acquired injury or disorder is sometimes known as symptomatic epilepsy. Almost any condition affecting the cerebral grey matter can result in epilepsy, but here only the more common forms of acquired epilepsy will be mentioned. The mode of diagnosis depends on the cause but MRI is a central investigation showing the site and location of the cerebral lesion and often providing reliable or near-reliable clues to pathology.

Hippocampal sclerosis

Hippocampal sclerosis is the most common cause of temporal lobe epilepsy [43–45]. It is found in up to one-third of patients with refractory focal epilepsy attending hospital clinics in whom there is no other structural lesion. However, it is less frequent in population-based cohorts and in patients with mild epilepsy. Hippocampal sclerosis typically causes complex partial seizures and the clinical features and symptom complex associated with the syndrome of mesial temporal lobe epilepsy. The pathogenesis of hippocampal sclerosis is probably multifactorial. There is a very clear association with a history of childhood febrile convulsions and one postulation is that the febrile convulsions, especially if

prolonged or complex, damage the hippocampus and result in hippocampal sclerosis. There is also evidence that, in some cases, hippocampal sclerosis may be a congenital lesion, and its frequent association with forms of cortical dysplasia (particularly subependymal heterotopia) adds some strength to the view that hippocampal sclerosis itself may sometimes be a form of cortical dysgenesis. The lesion is also common after severe brain trauma and in vascular damage.

Prenatal and perinatal injury

Epilepsy has traditionally often been thought to occur as a result of perinatal injury, although it is now recognized that many such cases have in fact genetic or other prenatal developmental pathologies causing the epilepsy. In most children with epilepsy, minor perinatal problems are quite irrelevant to the subsequent development of epilepsy, or indeed are themselves the result of the underlying defects. In controlled studies, only severe perinatal insults have been found to increase the risk of subsequent epilepsy, for example perinatal haemorrhage and ischaemic–hypoxic encephalopathy. Factors such as toxaemia, eclampsia, forceps delivery, being born with the 'cord round the neck', low birth rate or prematurity have only a very modest association, if any, with subsequent epilepsy (Table 3.5). Factors reported in some studies are not confirmed in others, but in one large case–control study, early

Table 3.5 Prenatal and perinatal risk factors for epilepsy. Measure is odds ratio for case–control studies and relative risk for cohort studies.

Parameter	Lilienfeld (1954, 1955) Pasamanick (1955)	Henderson (1964)	Chevrie (1977)	Rocca (1987)
Case ascertainment	Specialty clinics	Specialty clinics	Clinic	Medical records
Study design	Case–control	Case–control	Case–control	Case–control
Obstetric complications	1.62[a,c]/1.13[b,c]	1.7[b,c]	1.27[ns]	
Toxaemia, pre-eclampsia, eclampsia		0.99[b,c]		
Prematurity	2.3[a,d]/1.38[b,d]			
Pre- or perinatal abnormality			1.84[f]	
Low birth weight	4.9[a]/1.2[b]	1.4[b,c]		
Neonatal seizures		3.0[b,c]		ns[c]
Neonatal abnormalities (seizures, asphyxia)	1.6[a,c,d]/1.2[b–d]	9.3[b,c]	2.21[g]	
Small for gestational age				
Delivery problems		1.1[b,c]	1.74[g]	
Maternal haemorrhage	12.4[a]	3.6[b,c]		
Hypoxia				

From ref. 143, with permission.
[a] White only.
[b] Black only.
[c] Without associated defects (cerebral palsy, mental retardation, central nervous system malformations).
[d] Without maternal complications.
[e] Perinatal risk factors.
[f] $P < 0.01$.
[g] $P < 0.05$
ns, not significant

Table 3.5 *Continued*

Parameter	Bergamasco (1984)	Rantakallio (1986)	van den Berg (1969)	NCPP (1982–87)
Case ascertainment mothers	Delivery rooms	Birth cohort	Birth cohort	Pregnant
Study design	Historical cohort	Cohort	Cohort	Cohort
Obstetric complications		20		ns
Toxaemia, pre-eclampsia, eclampsia				ns
Prematurity				ns
Pre- or perinatal abnormality				
Low birth weight			2.1	ns
Neonatal seizures				22.4
Neonatal abnormalities (seizures, asphyxia)		5.6		
Small for gestational age			2.8	1.7
Delivery problems		17.4[a]		ns
Maternal haemorrhage				ns
Hypoxia	5.1			ns

[a] Perinatal risk factors.
NCPP, National Collaborative Perinatal Project; ns, not significant.
Measure is odds ratio for case–control studies and relative risk for cohort studies.

gestational age, vaginal bleeding during pregnancy, birth by Caesarean section and socioeconomic factors were found to confer a small risk of subsequent epilepsy [46–55].

Cerebral palsy

Cerebral palsy encompasses many pathologies, both prenatal and perinatal and both genetic and acquired. The term therefore has little specificity, although it is in widespread use. Whatever the cause, cerebral palsy is indicative of cerebral damage and thus is strongly associated with epilepsy. The US National Collaborative Perinatal Project, a prospective cohort study of infants followed to the age of 7 years, found epilepsy to occur in 34% of children with cerebral palsy: cerebral palsy was present in 19% of children developing epilepsy. In the same cohort, the risk of learning disability (associated with cerebral palsy) was 5.5 times higher among children developing epilepsy following a febrile seizure than in children with a febrile seizure alone. Learning disability (IQ < 70) was present in 27% of children with epilepsy, and seizures were present in about 50% of children with mental retardation and cerebral palsy.

Post-vaccination encephalitic encephalomyelitis

The possible role of vaccination (particularly pertussis vaccination) in causing a childhood encephalopathy and subsequent epilepsy and learning disability has been the subject of intense study, with contradictory claims [56]. There is a fairly general consensus now that the risk of vaccine-induced encephalopathy and/or epilepsy, if it exists at all, is extremely low. Risk estimates in the literature have included risk of a febrile seizure, 1:19496 vaccinations; risk of an afebrile seizure, 1:76133 vaccinations; risk of encephalopathy after pertussis infection, 0–3 cases per million vaccinations. The situation is complicated by the findings of a recent study which showed that encephalopathy in 11 out of the 14 children studied, although previously attributed to vaccination, was in fact due an inherited genetic defect of the *SCN1A* gene, which codes for the voltage-gated neuronal sodium channel [57]. Suggestions that MMR (mumps, measles, rubella) vaccine increases the risks of autism and epilepsy are now thought to be unfounded. Currently, the vaccine with the greatest risk is the smallpox vaccination, with a rate of 10–300 cases per million of post-vaccination encephalomyelitis, although safer vaccines are under development. The vaccines in which there is a possible association with post-vaccination encephalomyelitis are smallpox, measles, DPT (diphtheria, pertussis and tetanus), Japanese B encephalitis and rabies.

Degenerative diseases and dementia

Epilepsy is a common feature of degenerative neurological disease that involves the grey matter, but is seldom a leading symptom in pure leucodystrophy. Six per cent of persons over the age of 65 years have dementia, and the rate increases exponentially as a function of age [58,59]. Five per cent of patients with Huntington's disease have epilepsy, usually in the later stages. Epilepsy is more common in the juvenile form, and occasionally takes the form of a progressive myoclonic epilepsy. Epilepsy, and indeed status epilepticus, can be the presenting feature of Creutzfeldt–Jakob disease.

Post-traumatic epilepsy

Head trauma is an important cause of epilepsy [60–65]. Estimates of frequency of injury and of the risk of post-traumatic epilepsy have varied widely in different studies, partly because of different definitions and changes in diagnosis and management. The figures given below are best-guess estimates based on modern practice. It is customary to draw a distinction between open head injury, in which the dura is breached, and closed head injury, in which there is no dural breach. Post-traumatic seizures are traditionally subdivided into immediate, early and late categories. Immediate seizures are defined as those that occur within the first 24 h after injury, early seizures are those that occur within the first week and late seizures occur after 1 week. Early seizures occur in about 5% of all those admitted to hospital with head injury and are more common in children than in adults.

Closed head injuries are most common in civilian practice, usually from road traffic accidents, falls or recreational injuries. In different series, closed head injuries have accounted for between 2% and 12% of all cases of epilepsy [64]. Mild head injury – defined as head injury without skull fracture and with less than 30 min of post-traumatic amnesia – is, in most studies, not associated with any markedly increased risk of epilepsy. Moderate head injury – defined as a head injury complicated by skull fracture or post-traumatic amnesia for more than 30 min – is followed by epilepsy in about 1–4% of cases. Severe head injury – defined as a head injury with post-traumatic amnesia of more than 24 h, intracranial haematoma or cerebral contusion – is followed by epilepsy in about 10–15% of patients, in most studies. In a recent population-based study, the relative risk for epilepsy was 2.22 (95% CI 2.07–2.38%) in the presence of mild brain injury and 7.40 (95% CI 6.16–8.89%) in the presence of severe brain injury.

Post-traumatic epilepsy is much more frequent after open head injury [6]. This is particularly so in penetrating wartime injuries, with between 30% and 50% of patients suffering subsequent epilepsy. Overall, the risk of late epilepsy, if early epilepsy is present, is about 25% compared with 3% in patients who did not have early seizures. In patients admitted to hospital, the risk of late epilepsy is about 35% if there is an intracranial haematoma and about 5% if not, and about 17% if there is a depressed skull facture and 4% if not. If there is neither haematoma nor depressed skull fracture, the risk of epilepsy is 1% if there were no early seizures and 26% if there were early seizures. The risk of late epilepsy after open head injury is greatest if the extent of cerebral damage was large and involved the frontal or temporal regions. About 50–60% of patients have their first (late) seizure within 12 months of the injury, with most patients developing epilepsy within 4–8 months after the injury, and 85% within 2 years. There is a subsequent slight excess risk for 5 years.

The pathophysiology of post-traumatic epilepsy is complex and multifactorial. The kinetic energy imparted to the brain tissue produces pressure waves that disrupt tissue and lead to histopathological changes, including gliosis, axon retraction balls, wallerian degeneration, neurological scars and cystic white matter lesions. In addition, iron liberated from haemoglobin generates free radicals that disrupt cell membranes and have been impli-

Table 3.6 Postoperative epilepsy.

Procedure	Diagnosis	Number of patients	Patients with postoperative seizures		
			Patients without preoperative seizures (%)	Patients with preoperative seizures (%)	All patients
Burr hole	Glioma biopsy	186	9	67	25
	Shunt insertion	57	22	100	24
	Ventriculography	100	14	100	15
	All cases	343	13	69	22
Craniotomy	Glioma	115	20	70	34
	Intracranial haematoma	291	21	33	22
	Meningioma	61	22	56	36
Miscellaneous (subfrontal approach to sella lesions, other operations)		153	–	–	12

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cated in post-traumatic epileptogenesis. Iron and other compounds have also been found to provoke intracellular calcium oscillations. Hippocampal damage following head injury also seems common (over 80% of one series) and this may be due to enhanced excitability secondary to death of inhibitory dentate hilar neurones. Such hyperexcitability can last for months, following trauma, with reorganization of excitatory pathways, such as mossy fibre sprouting.

Epilepsy after neurosurgery

The incidence of seizures varies according to the nature of the underlying disease process, its site and its extent (Table 3.6) [66,67]. A large retrospective study found an overall incidence of 17% for postoperative seizures in 877 consecutive patients undergoing supratentorial neurosurgery for non-traumatic conditions. The patients had no prior history of epilepsy and the minimum follow-up was 5 years. The incidence of seizures ranges from 4% in patients undergoing stereotactic procedures and ventricular drainage to 92% for patients being surgically treated for cerebral abscess. The risk of craniotomy for glioma was 19%, for intracranial haemorrhage 21% and for meningioma removal 22%. All of these risks were greatly enhanced if seizures occurred preoperatively. Among patients developing postoperative seizures, 37% did so within the first postoperative week, 77% within the first year and 92% within the first 2 years. If early seizures occurred (i.e. those occurring in the first week), 41% of patients developed late recurrent seizures.

Studies after unruptured aneurysm show an overall risk of about 14%. The risk of a middle cerebral aneurysm resulting in epilepsy is 19%, and anterior communicating aneurysms and posterior communicating aneurysms carry a risk of about 10%. If the aneurysm has bled, causing an intracranial haematoma, the incidence of epilepsy is much higher, as it is if patients have perioperative complications including hemiparesis or meningitis, implying parenchymal damage. The overall postoperative risk of epilepsy depends on the site. In patients with no deficit, low-risk sites (risk under 5%) include aneurysms on the anterior communicating and posterior communicating arteries and a moderate risk (about 10%) in operations on the middle cerebral artery aneurysm. If there is a preoperative deficit, the risk of postoperative seizures increases to 20–30% in all these sites. An overall risk of epilepsy following shunt procedures is about 10%, although this depends on the site of the shunt insertion. As is the case following cerebral trauma, the risks of epilepsy following neurosurgery are greatest in the first postoperative year although a substantial proportion of cases (perhaps 25%) experience their first seizures in the second postoperative year.

Cerebral tumour

Brain tumours are responsible for about 6% of all newly diagnosed cases of epilepsy [68]. The rate is greatest in adults, and about one-quarter of adults presenting with newly developing focal epilepsy have an underlying tumour compared with less than 5% of children. Seizures occur in about 50% of all brain tumours. Metastases from non-CNS tumours often present with epilepsy or status epilepticus. The frequency of seizures is high in tumours in the frontal, central and temporal regions, lower in posterior cortically placed tumours and very low in subcortical tumours.

Glioma

Gliomas are the most common form of brain tumour causing epilepsy [69–71]. Slow-growing low-grade well-differentiated gliomas are the most epileptogenic lesions. In the Montreal series of 230 patients with gliomas, seizures occurred in 92% of those with oligodendrogliomas, 70% of those with astrocytomas and 37% of those with glioblastomas. Overall, slow-growing or benign tumours account for about 10% of all adult epilepsies, and fewer in children. The history of epilepsy will often have extended for decades, sometimes even into infancy. In chronic refractory tumoral epilepsy, oligodendrogliomas account for between 10% and 30%, dysembryoplastic neuroepithelial tumours (DNETs) account for 10–30%, astrocytomas account for 10–30%, gangliogliomas account for about 10%–20% and hamartomas for between 10% and 20%. These tumours are sometimes associated, particularly if situated in the temporal lobe, with hippocampal sclerosis.

Ganglioglioma

These are mixed tumours that are composed of neoplastic glial and neuronal cell types and constitute 10% of the neoplasms

removed at temporal lobectomy. Seizures are the primary presenting symptom in 80–90% of patients with gangliogliomas [72–75].

Dysembryoplastic neuroepithelial tumour

The dysembryoplastic neuroepithelial tumour (DNET or DNT) is a pathological entity only recently differentiated from other forms of 'benign gliomas'. They are, in fact, a relatively common cause of 'tumorous epilepsy', accounting for 10–30% of resected tumours in the temporal lobe [76–78].

Hamartoma

These benign tumours account for 10–20% of tumours removed at temporal lobectomy. These are more common in children. Their pathological features include proliferation of glial and neuronal elements, and they can be associated with other types of cortical dysplasia. Indeed the distinction between cortical dysplasia, hamartomas and relatively indolent neoplasms, such as DNET, can be blurred. The classic clinicopathological finding in *tuberous sclerosis complex* is the periventricular glial nodule or subependymal tuber. Histologically, these lesions are hamartomas and consist of foci of gliosis, which include both glial cells and neurones.

Hypothalamic hamartoma (and gelastic epilepsy)

The hypothalamic hamartoma is a particular form of hamartoma [79,80]. These are benign tumours, usually small and sometimes confined to the tuber cinereum. They develop in young children, and characteristically present with gelastic seizures, learning disability, behavioural disturbance and later with precocious puberty. They are diagnosed by MRI scanning but the lesions can be very subtle, especially if small, without mass effect and isodense on both T1 and T2 sequences.

Meningioma

Epilepsy is the first symptom of meningioma in 20–50% of cases. Meningiomas are more likely to cause epilepsy when located over the convexity, parasagittal/falx and sphenoid ridge, and with evidence of peritumoral oedema. There is no relationship between the presence of epilepsy and histological type.

Central nervous system infection

Central nervous system (CNS) infections are a major risk factor for epilepsy. Seizures can be the presenting or the only symptom, or one component of a more diffuse cerebral disorder [81,82].

Meningitis and encephalitis

The risk of chronic epilepsy following encephalitis or meningitis is almost seven times greater than that in the general population. The increased risk is highest during the first 5 years after infection, but remains elevated for up to 15 years. The risk is much higher after encephalitis [relative risk (RR) 16.2] than bacterial meningitis (RR 4.2) or aseptic meningitis (RR 2.3) [83].

The most common forms of bacterial meningitis are now due to *Streptococcus pneumoniae* (pneumococcal meningitis) and *Neisseria meningitidis* (meningococcal meningitis) [82,84]. *Haemophilus influenzae* type b (Hib) used to be a leading cause but new vaccines have virtually eradicated the condition in Western countries. Meningococcal meningitis is the most serious common form. Its incidence varies and in Europe, for instance, the highest incidence is in Scotland and Iceland. Ninety-five per cent of cases are due to serogroups B and C, and the case fatality rate is between 5% and 10%.

Table 3.7 Causes of infectious encephalitis.

Causes of infective encephalitis in the immunocompetent patient
Viral
Herpes simplex virus (HSV) type 1, other herpes virus (e.g. varicella, HSV type 2, CMV, EBV, HSV type 6), measles, mumps, rubella, rabies, arbovirus (e.g. Japanese B, St Louis, West Nile, equine and tick-borne virus), adenovirus, HIV, influenza (A,B), enterovirus, poliovirus
Bacterial and rickettsial (uncommon)
Bartonella spp., *Borrelia burgdorferi, Brucella* spp., *Leptospira interrogans, Listeria monocytogenes, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Rickettsia rickettsii*, Q fever and other rickettsial infections, *Treponema pallidum*, leptospirosis, *Nocardia actinomyces, Salmonella typhi, Legionella*
Protozoal (uncommon)
Malaria (*Plasmodium falciparum), Toxoplasma gondii*, *Naegleria fowleri, Acanthamoeba* spp.., cysticercosis, *Echinococcus* spp., *Trypanosoma* spp., schistosomiasis
Fungal (uncommon)
Blastomycosis, coccidioidomycosis, histoplasmosis, cryptococcus, aspergillosis, candidiasis
Causes of infectious encephalitis in the immunocompromised patient
Viral
Enterovirus, cytomegalovirus, HSV types 1,2,6, JC virus, measles, rubella, varicella
Protozoal
Amoebic meningoencephalitis, toxoplasmosis
Fungal
Cryptococcus neoformans, coccidioidomycosis, blastomycosis, histoplasmosis, *Aspergillus, Candida*

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Encephalitis is most commonly due to viral infection, but other infectious agents can cause post-encephalitic epilepsy (Table 3.7) [85]. The most common serious viral encephalitis is due to herpes simplex virus type 1 (HSV-1). The incidence of severe HSV-1 encephalitis is about 1 per million persons per year, but it is possible that more minor infection occurs which escapes detection. It is often assumed that the many cases of epilepsy, currently considered cryptogenic, are due to occult viral infection – although hard evidence in support of this point is entirely lacking. Viral encephalitis needs to be differentiated from acute disseminated encephalomyelitis (ADEM), which can present with a very similar picture, and also from the increasingly recognized autoimmune encephalopathies, particularly those associated with voltage-gated potassium channel antibodies or antithyroid antibodies (Hashimoto's disease).

Patients with acquired immunodeficiency syndrome (AIDS) and other immunocompromised states have a different range of pathogens, and cerebral infection is a common feature of the condition; the most common opportunistic CNS infections are cryptococcal meningitis, toxoplasmosis, tuberculosis and cytomegalovirus (CMV) encephalitis [83,86,87]. Seizures may also be

a sign of progressive multifocal leucoencephalopathy in human immunodeficiency virus (HIV), although usually a minor aspect of the clinical presentation.

Cerebral malaria

Seizures and typically status epilepticus are particularly common in the acute phase of cerebral malaria [88–90]. Chronic epilepsy is common after cerebral malaria, particularly if seizures occurred in the acute phase, and one study has shown a 9- to 11-fold (CI 2–18) increase in risk of epilepsy in children with malaria compared with children without malaria. This risk is at least double the risk of epilepsy after complex febrile seizures.

Pyogenic cerebral abscess

Pyogenic cerebral abscess is an uncommon but serious cause of infective epilepsy [91]. Abscesses range in size from microscopic foci of inflammatory cells to major encapsulated necrotic areas of a cerebral hemisphere exerting significant mass effect. The species of bacteria responsible for brain abscess depends on the pathogenic mechanism involved. Commonly isolated organisms are streptococci, including aerobic, anaerobic and microaerophilic types. *S. pneumoniae* is a rarer cause of brain abscesses, which are often the sequel to occult cerebrospinal fluid (CSF) rhinorrhoea and also to pneumococcal pneumonia in elderly patients. Enteric bacteria and *Bacteroides* are isolated in 20–40% of cases and often in mixed culture. Anaerobic organisms have become increasingly important organisms and in many instances more than a single bacterial species is recovered. Gram-negative bacilli rarely occur alone. Staphylococcal abscesses account for 10–15% of cases and are usually caused by penetrating head injury or bacteraemia secondary to endocarditis. Clostridial infections are most often post-traumatic. Rarely, *Actinomyces* or *Nocardia* species are the causative agents in a brain abscess.

Neurocysticercosis

Worldwide, neurocysticercosis (NCC) is the most common parasitic disease of the CNS and it is a major cause of epilepsy in endemic areas such as Mexico, India and China. Epilepsy is the most common clinical manifestation and a usual presenting feature of NCC [92–94]. The condition is a helminthiasis caused by the encysted larval stage, *Cysticercus cellulosae*, of the pork tapeworm *Taenia solium*. Parenchymal cysts usually lie dormant for many years and symptoms usually coincide with larval death and an intense inflammatory response caused by the release of larval antigens. The solitary cerebral parenchymal lesion is a common form of presentation, but lesions are often multiple. Over time, the cysts shrink progressively and then calcify or disappear completely. Seizures are the most common symptom and develop when a cyst is degenerating or around a chronic, calcified lesion. In the racemose form of NCC, the cysts can obstruct CSF flow and present with mass effect, hydrocephalus or basal arachnoiditis. Diagnosis is made by imaging and by serological tests. The results of CSF and EEG examination are rather non-specific. Newer enzyme-linked immunoelectron transfer blot (EITB) assays on CSF or serum appear to have higher sensitivity (98%) and specificity (100%) in multiple cysticercosis. Its superiority to enzyme-linked immunosorbent assay (ELISA) is due to its ability to detect up to seven glycoproteins specific to *T. solium*. Recently, an antigen detection ('capture') assay specific for viable metacestodes in CSF has been designed.

Tuberculoma

Tuberculosis remains a major problem in developing countries and the incidence is also rising in industrialized countries, with increasing migration and also the spread of HIV. The most common form of tuberculosis is pulmonary infection, and the incidence of intracranial tuberculoma (tuberculous abscess) has decreased, particularly in Western countries, owing to the BCG vaccination programme. In the early twentieth century, tuberculomas accounted for about one-third of all space-occupying lesions. The incidence fell dramatically throughout the century, although recently rising again. For example, today, tuberculomas account for about 3% of all cerebral mass lesions in India, and 13% of all cerebral lesions in patients with HIV [95,96]. Diagnosis depends on the clinical context, imaging, serology, and histological examination of biopsy material.

Cerebrovascular disease

Epilepsy can complicate all forms of cerebrovascular disease. Stroke is the most commonly identified cause of epilepsy in the elderly, and occult stroke also explains the occurrence of many cases of apparently cryptogenic epilepsies in aged individuals. A history of stroke has been found to be associated with an increased lifetime occurrence of epilepsy [odds ratio (OR) 3.3; 95% CI 1.3–8.5]. Among the other vascular determinants, only a history of hypertension was associated with the occurrence of unprovoked seizures (OR 1.6, 95% CI 1.0–2.4) [97,98]. The risk of unprovoked seizures rises to 4.1 (95% CI 1.5–11.0) in subjects having a history of both stroke and hypertension [99]. Status epilepticus occurs in the acute phase of about 1% of all strokes, and 20% of status epilepticus is due to stroke.

Cerebral haemorrhage

The reported risk of chronic epilepsy due to intracranial haemorrhage has varied greatly from series to series, but is generally in the region of 5–10%. The incidence of early epilepsy (seizures in the first week) is higher, up to 30% in some series with status epilepticus in about 10%. Early seizures do not necessarily lead to chronic epilepsy, although they increase the long-term risk, and about one-third of those with early seizures continue to have a liability to epilepsy. Epilepsy is common after large haemorrhages and haemorrhages which involve the cerebral cortex: they are less common in deep haematomas and rare after subtentorial haemorrhage. The epilepsy almost always develops within 2 years of the haemorrhage. The risk of seizures after subarachnoid haemorrhage is approximately 25% and has been claimed to be independent of residual deficit. If early seizures occurred, the risk of subsequent epilepsy is over 70% [100,101].

Cerebral infarction

After cerebral infarction, epilepsy occurs in about 6% of patients within 12 months and 11% within 5 years of the stroke [97,98]. Epilepsy is more common in cerebral infarcts located in the anterior hemisphere, and involving cortex. The standardized mortality ratio (SMR) for epilepsy after infarction has been found to be

5.9 (95% CI 3.5–9.4), and the risk of developing seizures is highest during the first year, and higher if there is a history of recurrent stroke. In a multivariant analysis, early seizures and recurrent strokes were the only clinical factors shown to predict the occurrence of epilepsy after infarction. The risk of epilepsy is about 17–20 times greater than in non-stroke control subjects. As in head injury, the occurrence of early seizures results in a greater (8–16×) increase in risk of subsequent epilepsy than in patients with stroke and no early seizures, and about 35% of those with early seizures develop subsequent epilepsy. Other factors associated with a greater risk of epilepsy in various studies are severity, size of infarct, haemorrhagic transformation, cortical versus subcortical site of the stroke and, in some studies, an embolic stroke.

Occult degenerative cerebrovascular disease

Epilepsy can also complicate occult cerebrovascular disease [3]. Late-onset epilepsy can be the first manifestation of cerebrovascular disease. Between 5% and 10% of patients presenting with stroke have a history of prior epileptic seizures in the recent past, and, in the absence of other causes, new-onset seizures should prompt a screen for vascular risk factors [102].

Arteriovenous malformations

An arteriovenous malformation (AVM) is a racemose network of arterial and venous channels that communicate directly, rather than through a capillary bed [103]. Between 17% and 36% of supratentorial AVMs present with seizures [104], with or without associated neurological deficits, and 40–50% with haemorrhage. Smaller AVMs (<3 cm diameter) are more likely to present with haemorrhage than large ones. Conversely, large and/or superficial malformations are more epileptogenic, as are AVMs in the temporal lobe. About 40% of patients with large arteriovenous malformations have epilepsy, and epilepsy is the presenting symptom in about 20%. Irrespective of the initial presentation, a significant proportion of patients with cerebral AVMs will develop epilepsy after diagnosis. The risk of seizures seems to be higher the younger the patient is at the time of diagnosis. In one study, among patients aged between 10 and 19 years, there was a 44% risk of epilepsy by 20 years. This risk declined to 31% for patients aged 20–29 years and to 6% for patients aged 30–60 years. The annual risk of bleeding of an AVM is in the region of 2–4%, irrespective of whether the malformation presented with haemorrhage, and the average mortality is about 1% per year. The risk is dependent on the size of the AVM, its growth, the presence of aneurysms, the type of feeding and draining vessels and the anatomy. The risk of surgical resection depends on the anatomy, size and site of the AVM, and is potentially hazardous: endovascular therapy and focused radiotherapy are also used. Arteriovenous malformations also show highly characteristic MRI appearances, with high signal on T2-weighted images often with a notch-like configuration, and areas of decreased signal intensity representing previous intralesional bleeding.

Cavernous haemangioma

Cavernous haemangiomas (cavernoma) are well-circumscribed hamartomatous lesions consisting of irregularly walled sinusoidal vascular channels. They are located within the brain but without intervening neural tissue and have large feeding arteries or draining veins. Pathologically, they consist of endothelial cell-lined caverns filled with blood and surrounded by a matrix of collagen and fibroblasts. They have the potential to haemorrhage, calcify or thrombose and are multiple in 50% of cases. They account for 5–13% of vascular malformations of the CNS and are present in 0.02–0.13% of autopsy series. The majority of these lesions present in the third and fourth decades of life, but 20–30% present earlier in childhood or early adult life. Cavernomas can increase in size and number over time, particular in genetically determined cases and in those in whom cavernoma have developed after cerebral irradiation. However, in most cases, the factors influencing the development of new lesions or growth of existing lesions are unknown. At least 15–20% of patients remain symptom free throughout their lives. Patients present with seizures (40–70%), focal neurological deficits (35–50%), non-specific headaches (10–30%), and cerebral haemorrhage [105,106]. Retinal, skin, and liver lesions have occasionally been reported, presumably on a genetic basis. Familial clustering can be found in 10–30% of cavernous haemangiomas and familial cases have been found to be linked to genes at three different loci: the *CCM1, CCM2* and *CCM3* genes. Overall, 40% of familial cases are linked to *CCM1*, with higher rates among Hispanic cases. Genetic testing is available. The lesions are usually diagnosed on MRI, whereas cerebral angiography often shows no abnormality. On T2-weighted images the typical appearance of cavernomas is that of a reticulated core of mixed signal representing blood in various states of degradation surrounded by a hypointense haemosiderin halo. T1 images show a similar pattern but they are less sensitive. There is slight contrast enhancement in some cases.

Other vascular disorders

Cortical venous infarcts are particularly epileptogenic, at least in the acute phase, and may underlie a significant proportion of apparently spontaneous epileptic seizures complicating other medical conditions and pregnancy, for instance. Seizures also occur with cerebrovascular lesions secondary to rheumatic heart disease, endocarditis, mitral valve prolapse, cardiac tumours [107] and cardiac arrhythmia, or after carotid endarterectomy. Infarction is also an important cause of seizures in neonatal epilepsy. Epilepsy is also common in eclampsia, hypertensive encephalopathy and malignant hypertension and in the anoxic encephalopathy which follows cardiac arrest or cardiopulmonary surgery. Unruptured aneurysms occasionally present as epilepsy, especially if large and if embedded in the temporal lobe, for example a giant middle cerebral or anterior communicating aneurysm. Epilepsy with a vascular basis also occurs in antiphospholipid syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), Moyamoya disease, collagen disease (e.g. Ehlers–Danlos syndrome, Marfan's syndrome), Behçet's disease and amyloid angiography. Other rare causes of epilepsy include temporal arteritis, polyarteritis nodosum, Takayasu's disease, Fabry's disease and the hyperviscosity syndrome.

Other neurological disorders

Rasmussen's encephalitis

Rasmussen's encephalitis is a rare progressive neurological disorder of unknown cause. Pathologically, there is severe unilateral hemisphere atrophy with histological evidence of perivascular lymphocytic infiltration, neuronal loss and microglial nodule formation. The pathological changes are strikingly unilateral and, where changes do occur in the opposite hemisphere, these are usually minor [108–110]. The cause is unclear, although viral and immunological factors have been implicated. The genomes of various viruses have been found in biopsy tissue, including the Epstein–Barr and herpes simplex viruses, and IgG, IgA and C3 have been found. Glu-R3 antibodies have been reported in the sera of some patients. None of these findings though appears to be consistently present. Diagnosis is on the basis of the clinical and MRI findings.

Demyelinating disorders

Several clinical series reported an association between epilepsy and multiple sclerosis (MS). In one small population-based study from Iceland, patients with multiple sclerosis had a threefold but non-significant increase (SMR 3.0; 95% CI 0.6–8.8) in the risk of epilepsy compared with the general population [111]. In another series, the cumulative risk of epilepsy in patients with multiple sclerosis was found to be 1.1% at 5 years, 1.8% by 10 years and 3.1% by 15 years. The mean interval until the onset of epilepsy is about 7 years after the onset of multiple sclerosis [111,112].

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disorder that can follow systemic infections, and it is immunologically mediated. Epilepsy is a feature of the acute attack and occurs much more commonly than in an acute attack of MS. ADEM can follow infections with many different viruses (notably measles, mumps, rubella, varicella, HIV, hepatitis A and B, Epstein–Barr and CMV) or other infectious agents (notably mycoplasma, *Streptococcus*, *Borrelia*, *Campylobacter*, *Chlamydia*, *Leptospira* and *Legionella*). The incidence after measles infection is about 1 in 1000, varicella infection 1 in 10 000 and rubella infection 1 in 20 000.

Inflammatory and immunological diseases of the nervous system

Epilepsy can be a complication of many inflammatory and immunological diseases affecting the CNS. The mechanisms of seizures can be a result of the direct effect of immunological processes (for instance in Rasmussen's encephalitis) or an indirect effect owing to vascular disease and cerebral infarction (for instance, in the cerebral vasculitides). In many conditions, the mechanisms are unknown. Epilepsy is a common symptom of all forms of cerebral vasculitis, and particularly in systemic lupus erythematosus. It occurs less often in other vasculitides such as Behçet's disease and in other 'connective tissue disorders', such as Sjögren's syndrome and mixed connective tissue disease. In SLE, seizures occur in about 25% of cases and are particularly common in severe or chronic cases and in lupus-induced encephalopathy. Seizures can also occur as the presenting and only symptom of SLE [113]. Epilepsy can occur in all other forms of large, medium or small vessel vasculitis, sometimes on the basis of infarction. Chronic epilepsy seems to be a particularly common sequel of Henoch–Schönlein purpura, probably on the basis of acute vasculitis. Seizures are the most common neurological complication of the inflammatory bowel diseases (ulcerative colitis and Crohn's disease), occurring in one series in 6% of cases. The epilepsy may be a direct effect or caused indirectly by dehydration or sepsis. Neurological complications occur in about 10% of patients with Whipple's disease, and the condition presents neurologically in 5%. In a series of cases with neurological symptoms, myoclonus occurred in 25% and seizures in 23%. About 10% of patients with coeliac disease have neurological symptoms, and epilepsy is associated with several rather distinctive neurological presentations. Epilepsy in association with occipital calcification can be the presenting symptom of coeliac disease. Epilepsy, myoclonus and cerebellar ataxia or spinocerebellar degeneration, and sometimes dementia is another characteristic neurological syndrome. Myoclonus and seizures are also a prominent feature of Hashimoto's thyroiditis, a relapsing encephalopathy associated with high titres of thyroid antibody [114]. Epilepsy is also a feature, although often not prominent, of the primary granulomatous diseases of the CNS such as sarcoidosis.

There has been recent interest in the occurrence of epilepsy, particularly in the syndrome of limbic encephalitis, associated with high titres of antibodies against voltage-gated potassium channels (VGKCs) [115–117]. The epilepsy usually presents as a subacute illness, associated also with psychosis, neurological signs (e.g. ataxia), memory loss and behavioural change. Other cases of limbic encephalitis have no detectable antibody present (although it is assumed that the cause is immunologically mediated, by an unknown antibody) and some are paraneoplastic. It also remains possible that some chronic temporal lobe epilepsy cases are also due to immune-mediated mechanisms. This is an area of intense research interest.

Seizure precipitants

The precipitant of a seizure can be defined as a factor that, in patients with pre-existing epilepsy, precedes the onset of the attack and is considered to be an explanation of why the seizure happened when it did and not earlier or later. A detailed consideration of these factors is outwith the scope of this chapter. About 50–60% of people with epilepsy claim that precipitants are sometimes identifiable, and the most common factors are listed in Table 3.7. Attention to these factors can dramatically improve seizures in susceptible persons, and this is particularly true of avoidance of alcohol, sleep deprivation and stress.

The reflex epilepsies

The term reflex epilepsy is used to describe cases in which seizures are evoked consistently by a specific environmental trigger. In some cases, the stimulus can be highly specific and in others less so. The term is not usually applied to patients whose seizures are precipitated by internal influences such as menstruation, nor to situations where the precipitating factors are vague or ill-defined (e.g. fatigue, stress), nor to patients with existing epilepsy in

which seizures are more likely to occur as a result of specific precipitants (e.g. sleep deprivation, alcohol); transitional cases, however, occur in what can be a nosological grey area. The reflex epilepsies are sometimes subdivided into simple and complex types. In the simple forms, the seizures are precipitated by simple sensory stimuli (e.g. flashes of light, startle) and in the complex forms they are precipitated by more elaborate stimuli (e.g. specific pieces of music). The complex forms are much more heterogeneous and the syndromes are less well defined than the simple reflex epilepsies. In hospital practice, about 5% of patients show some features of reflex epilepsy. The stimuli most reported to cause seizures include flashing lights and other visual stimuli, startle, eating, bathing in hot water, music, reading and movement.

Visual stimuli, photosensitivity and photosensitive epilepsy

The most common reflex epilepsies are those induced by visual stimuli. Flashing lights, bright lights, moving visual patterns (e.g. escalators), eye closure, moving from dark into bright light, and viewing specific objects or colours have all been described to induce seizures [118–127]. The term photosensitive epilepsy should be confined to those individuals who show unequivocal electroencephalographic evidence of photosensitivity, and differentiated from other, usually more complex, cases in which seizures can be apparently precipitated by visual stimuli but when electroencephalographic evidence of photosensitivity cannot be demonstrated. Photosensitivity (strictly defined) is present in a population with a frequency of about 1.1 : 100 000 persons, and 5.7 : 100 000 in the age range of 7–19 years, and very strongly associated with epilepsy. About 3% of persons with epilepsy are photosensitive and have seizures induced by photic stimuli (usually viewing flickering or intermittent lights or cathode ray monitors, bright lights or repeating patterns). Most patients with photosensitivity have the syndrome termed idiopathic generalized epilepsy, although photosensitivity also occurs in patients with focal epilepsy arising in the occipital region, and some inherited metabolic diseases, and occasionally in other epileptic conditions.

Startle-induced epilepsy

Startle-induced seizures usually occur in patients with a frontal or central focus and usually in lesional epilepsy [128]. The seizures usually take a form similar to a tonic seizure, and the EEG is commonly normal or shows rather non-specific changes. A susceptibility to startle is more common in late childhood and adolescence and may resolve as the patient gets older.

Primary reading epilepsy

Primary reading epilepsy is a specific rare epilepsy syndrome in which clonic jerking of the jaw or perioral muscles, which can evolve to a generalized convulsion, is precipitated by prolonged reading. Some forms may be variants of idiopathic generalized epilepsy [129,130].

Other forms of reflex epilepsy [3]

Other simple reflex epilepsies include cases with seizures induced by movement, touching or tapping. These should be differentiated from paroxysmal kinesogenic choreoathetosis and stimulus-sensitive myoclonus. Hot-water epilepsy, which is common in parts of India but rare elsewhere, is a remarkable syndrome in which seizures are induced by pouring of hot water over the head or immersion in hot water [131]. Complex forms of reflex epilepsies include cases in which seizures are precipitated by the act of eating, hearing certain sounds, hearing certain pieces of music and psychic processes including decision-making, mental arithmetic, chess playing, card playing, drawing, spatial construction and deep thought [132]. These conditions are heterogeneous in terms of aetiology, electroencephalography and seizure types. The mechanisms underlying these (and other) reflex epilepsies are uncertain and specific 'reflex arcs' have not been identified. Prevention of the precipitating cause is sometimes helpful, as is drug treatment along conventional lines.

Acute symptomatic seizures

Acute symptomatic seizures, a somewhat unsatisfactory term, is reserved for seizures in persons who had not previously had seizures, which start in close temporal association to a sudden acute precipitant [133,134]. If the epilepsy can be attributable to a pre-existing, non-acute or static cause it is referred to as remote symptomatic epilepsy but clearly there is a grey area in which the distinction between acute and remote symptomatic epilepsies is rather arbitrary. The boundary is similarly blurred in some cases of reflex epilepsy or cases in which seizures have acute precipitants, such as sleep deprivation or alcohol. Furthermore, if seizures continue after the acute phase, and if the cause remains present (e.g. post-stroke, post-traumatic, tumoral or post-infectious epilepsy), seizures that were initially categorized as acute symptomatic are reclassified as remote symptomatic. All this makes rather a nonsense of the classification scheme.

The age-adjusted incidence rate of symptomatic seizures, reported in an old study from the record-linkage system in Rochester, Minnesota, was about 40 per 100 000 person-years. The rate was higher in men than in women (52 versus 29 per 100 000 per year), and highest in the first year of life owing to metabolic, infectious and encephalopathic aetiologies. The rate decreases in childhood and early adulthood, with a nadir at 25–34 years, and then increases, producing a second peak at age 75 and older, accounted for mostly by cerebrovascular disorders. The cumulative incidence of acute symptomatic seizures has been estimated to be about 4% up to the age of 80 years.

Metabolic- and endocrine-induced seizures

Many types of metabolic or endocrine disturbances can result in epilepsy [135]. Hyponatraemia is the most common electrolyte disturbance to result in seizures, which typically occur if the serum sodium level falls below 115 mmol/L. Seizures also routinely occur in the presence of hypernatraemia, hypocalcaemia, hypercalcaemia, hypomagnesaemia, hypokalaemia and hyperkalaemia. Ten per cent of patients with severe renal failure have seizures, caused either by the metabolic disturbance, renal encephalopathy, dialysis encephalopathy or dialysis disequilibrium syndrome. Asterixis may develop into myoclonus and then epilepsy.

Seizures are a common occurrence in hepatic failure. Hepatic encephalopathy may be overlooked and routine liver function

tests can be relatively normal; hyperammonaemia is sometimes diagnostically helpful. Reye's syndrome should be considered in patients with liver failure, especially in children, in whom it is associated with aspirin intake.

Hypoglycaemia is a potent cause of seizures, which can occur if the blood sugar levels fall below 2.2 mmol/L. This is commonly a result of insulin therapy in patients with diabetes but can also be due to insulinoma and drugs such as quinine and pentamidine. Non-ketotic hyperglycaemia frequently causes seizures. Levels of blood sugar as low as 15–20 mmol/L can cause seizures if there is associated hyperosmolarity. The seizures in non-ketotic hyperglycaemia are focal and this implies the presence of cerebral pathology (usually cerebrovascular disease). Diabetic ketoacidosis does not frequently result in seizures.

Thyroid disease can result in seizures that are due either to immunological mechanisms, or directly to hormonal change or hormonally induced metabolic change. Twenty per cent of patients with severe myxoedema have seizures. Hashimoto's encephalopathy, a steroid-responsive encephalopathy associated with high levels of antithyroid antibody, is an immunologically determined condition that results in altered consciousness, focal signs and other features of encephalopathy, including myoclonus and tonic–clonic seizures.

Alcohol- and toxin-induced seizures

Alcohol abuse is a potent cause of acute symptomatic seizures, and indeed of epilepsy, in many societies [136–138]. There are various mechanisms. Binge drinking can result in acute cerebral toxicity and seizures. Alcohol withdrawal in an alcohol-dependent person carries an even greater risk of seizures. Withdrawal seizures occur typically in a tonic–clonic form, occurring 12–24 h after withdrawal, and are associated with photosensitivity. Seizures can also be caused by the metabolic disturbances associated with binge drinking (notably hypoglycaemia, hyponatraemia and hepatic failure), cerebral damage owing to trauma, cerebral infection, subdural haematoma, chronic neurotoxic effects of chronic alcohol exposure or acute Wernicke's encephalopathy due to thiamine deficiency. It has been estimated that 6% of patients with alcoholism investigated for epilepsy have an additional identifiable causative lesion.

The risk of a first generalized tonic–clonic seizure in chronic alcoholics is seven times greater than in non-alcoholic control subjects, and in the USA, for instance, 15% of patients with epilepsy have alcoholism. The risk of seizures is increased only with a daily alcohol intake of 50 g/day or more, and the higher the intake the higher the risk. Odds ratios according to alcohol intake have been calculated to be 3.0 (95% CI 1.7–5.4) for a daily intake of 51–100 g/day, 7.9 (95% CI 2.9–21.9) for 101–200 g/day, and 16.6 (95% CI 1.9–373.4) when the intake is more than 200 g/day.

Seizures can also be provoked by exposure to many different toxins. Potent causes include heavy metal poisoning and carbon monoxide poisoning (in which carboxyhaemoglobin levels are above 50%). Although acute toxic exposure causes seizures, these are usually part of an acute encephalopathy. Whether low-grade long-term exposure to carbon monoxide, lead or to other heavy metals carries any risk is quite unclear. To what extent organophosphate poisoning can result in seizures is equally contentious, and reliable data seem to be absent.

Drug-induced seizures

A wide range of drugs, toxins and illicit compounds can cause acute symptomatic seizures and epilepsy, although seizures accounted for less than 1% of 32 812 consecutive patients prospectively monitored for drug toxicity [139–141]. As many as 15% of drug-related seizures present as status epilepticus. In a population-based survey from Richmond, Virginia, drug overdose was the reported cause in 2% of children and 3% of adults with status epilepticus. Drugs can cause seizures if the following conditions are present: intrinsic epileptogenicity, patient idiosyncrasy, antiepileptic drug interactions, impairment of the hepatic or renal drug metabolism, drug withdrawal phenomena and direct cerebral toxicity (especially in an intentional overdose). Some authorities also include febrile seizures in this category but others do not.

Almost any psychotropic drug carries a risk of inducing seizures. The risk is highest with the aliphatic phenothiazines [e.g. chlorpromazine (1–9% risk), promazine or trifluoperazine]. The use of clozapine is associated with a 1–4% risk of seizures and with interictal epileptiform abnormalities. The piperazine phenothiazines (acetophenazine, fluphenazine, perphenazine, prochloperazine and trifluoperazine), haloperidol, sulpiride, pimozide, thioridazine and risperidone are thought to have the lowest epileptogenic potential, although firm data are lacking. The risk of seizures with antidepressant drugs ranges from <1% to 4% and varies with the drug category. Agents accompanied by a high risk of seizures include clomipramine and the second-generation antidepressants amoxapine, maprotiline and bupropion. The risk of seizures with tricyclic antidepressants (other than clomipramine), citalopram, moclobemide and nefazodone is thought to be lower. The seizure risk with the selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine), monoamine oxidase inhibitors and trazodone is probably lower although definitive data are lacking. All of these drugs in overdose carry a significant (>10%) risk of seizures. The narcotic analgesic meperidine is metabolized in the liver to normeperidine, a potent proconvulsant, which tends to accumulate after prolonged administration and renal failure. The monocyclic antidepressant bupropion, which is used to assist the cessation of smoking, provokes seizures in 1 in 1000 patients. Pethidine can also result in seizures, especially in the presence of renal impairment or in combination with monoamine oxidase inhibitor (MAOI) drugs. Lidocaine-related neurotoxicity is common with intravenous use, especially with advanced age, congestive heart failure, shock, and renal and hepatic failure. The anaesthetics enflurane, propofol and isoflurane can be proconvulsant. Quinine and the other antimalarial drugs, especially mefloquine, can provoke acute seizures, and are relatively contraindicated in epilepsy. Various traditional remedies, including morning primrose oil and some Chinese and Indian herbal medicines, can provoke seizures.

Neurotoxic reactions may occur frequently with β-lactam antibiotics (semisynthetic penicillins and cephalosporins), probably due to GABA antagonist action. Benzylpenicillin, cefazolin and imipenem/cilastatin have the higher neurotoxic potential (with increased risk at higher doses) in the presence of renal failure, blood–brain barrier damage, pre-existing CNS disorders, comedication with nephrotoxic agents or drugs lowering seizure threshold. Isoniazid can be induced by antagonizing pyridoxal phosphate (the active form of pyridoxine), which is involved in

GABA biosynthesis. Seizures have also been reported, especially in elderly patients, in relation to aminoglycosides, metronidazole, quinolones and amantadine. Quinolones (nalidixic acid, norfloxacin, ciprofloxacin) probably enhance seizure activity by inhibiting GABA binding to membrane receptors. The tetracyclines seem less proconvulsant than these other antibiotics. Zidovudine and other antiviral agents have caused seizures in patients with HIV. Seizures (and non-convulsive status epilepticus) have been reported after administration of intravenous contrast media, and the risk is as high as 15% in patients with brain metastases.

The anti-cancer chemotherapeutic agents can provoke seizures, especially chlorambucil (95%), and ciclosporin (1–3%), asparaginase, tacrolines and busulfan, but also the platin drugs, vinca alkaloids, bleomycin, anthracyclines and azathioprine.

Theophylline is a potent convulsant that can result in seizures or status epilepticus, possibly as a result of the antiadenosine action. β-Blockers and other antiarrhythmic agents have been reported to precipitate seizures, particularly in overdose. Cimetidine, levodopa, insulin, thiazide diuretics, lidocaine, salicylates, chemotherapeutic agents, L-asparaginase and baclofen have been reported to cause seizures. The non-steroidal analgesics also predispose to seizures [for example, non-steroidal antiinflammatory drugs (NSAIDs), tramadol, diamorphine and pethidine].

Seizures may be precipitated after sudden withdrawal of any antiepileptic drug but seem a particular problem in benzodiazepines, carbamazepine and barbiturate withdrawal.

Recreational drugs can cause seizures. The greatest risk is with the stimulant drugs, such as cocaine, amphetamine and 'ecstasy' (3,4-methylenedioxymethamphetamine, MDMA). The hallucinogens, such as phencyclidine (angel dust) and lysergic acid diethylamide (LSD), less commonly cause seizures. The opiates and the organic solvents are least epileptogenic, although past or present heroin use has been shown to be a risk factor for provoked and unprovoked seizures (OR 2.8; 95% CI 1.5–5.7). Of the performance-enhancing drugs, erythropoietin has strong epileptogenic potential. By contrast, in one study, marijuana use in men was shown to have a protective action against non-provoked seizures (OR 0.4; 95% CI 0.2–0.8) and provoked seizures (OR 0.2; 95% CI 0.1–0.8).

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4 Differential Diagnosis of Epilepsy

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Introduction

Episodic disorders of consciousness or behaviour are a common cause of visits to emergency departments, family physicians and neurologists. Although the diagnosis of an epileptic disorder may be straightforward, it is frequently difficult, especially if the event is unwitnessed, or if the history is incomplete. Among the wide variety of neurological and non-neurological conditions that may be mistaken for epilepsy, the most frequent and challenging distinction is between epileptic events and syncope or presyncope.

In my experience, 20–30% of new patients attending a specialty epilepsy clinic have a diagnosis other than epilepsy. A number of studies have shown that syncope is commonly misdiagnosed as epilepsy, largely through ignorance of the complex prodrome that may occur, and the sometimes dramatic nature of a clinical event that shares many features with epileptic convulsions [1]. Migraine, non-epileptic seizures (pseudoseizures), hyperventilation and vertigo are other conditions commonly misdiagnosed as epilepsy. Less common disorders that are confused with epilepsy include cerebral ischaemia or paroxysmal symptoms of demyelinating disease, raised intracranial pressure, Tourette's syndrome and other movement disorders. Patients presenting with behavioural symptoms most often have a primary psychiatric diagnosis but are often thought to be suffering a seizure disorder. The surprising abundance of misdiagnosed epilepsy has been confirmed in a number of studies, and is cause for much concern [2].

Epilepsy remains primarily a clinical diagnosis. The incorrect diagnosis is often catastrophic for the patient, resulting in significant restriction to social activity and employability, as well as administration of unnecessary medication, with all the problems that entail. Loss of driving privileges is often the most immediate and traumatic component for patients whose livelihood may depend on a valid driving licence. From all perspectives, the diagnosis of epilepsy requires clinical skill and judgement, and it is incumbent on the clinician to attach a definite diagnosis only if certain.

General approach to episodic disturbances

As an enormous variety of conditions can cause episodes of transiently disturbed consciousness or function, the major component of clinical management consists of separating out the various causes, usually on clinical grounds. Determining the nature of events can be very challenging, particularly when the event has been unwitnessed or when the patient is an inadequate historian.

Obtaining a clear account of the nature of the attack is the most important single component of the assessment. Ascertain precisely the circumstances of the event, any warning that occurred, the duration of the attack, exactly what occurred during the event, the nature and speed of recovery and as well as whether there were any focal or lateralizing signs after the event. There is no substitute for a detailed history of the attack from both the patient and any eye-witnesses, and obtaining a detailed account of the circumstances of the event as well. What was the patient engaged in the day and evening prior to the event? Was there sleep deprivation or were there other medical problems? Was there unusual stress or anxiety [3]? Obtaining an eye-witness account is crucial and the telephone is now an invaluable device in this regard, particularly now mobile telephones are so widely owned (half the world's population at last count, many with video-cameras). Dramatic disparity is often noted between the eye witness's and patient's stories. Whereas the patient may recall a simple fall or brief loss of consciousness, an eye-witness may provide a detailed account of generalized convulsion with postictal confusion, tongue biting and so on, for which the patient is often amnesic. In other situations there may be deliberate concealment. Clinical examination may provide useful information, particularly if undertaken in the hours after the event, but is most often non-contributory. Supportive investigations including electroencephalograms (EEGs) and structural imaging may provide additional evidence for the diagnosis, but interpreting all these factors requires clinical skill and judgement. EEGs are often normal interictally in the adult patient with epilepsy and, conversely, on interictal traces around 20% of people have minor and irrelevant abnormalities that are frequently misinterpreted as confirming a diagnosis of epilepsy.

Events that occur in particular circumstances should always raise the suspicion of syncope. There are obvious causes, such as sudden pain, venesection, emotion, standing for long periods or watching unpleasant movies. However, mechanical causes, such as cough, urination or defecation, may also provoke syncope; the differences between syncope and epilepsy are detailed below. Episodes of loss of consciousness occurring with postural change are more likely to be syncopal. Shock, fright or extreme emotion can precipitate syncope also but these are frequently recognized to be non-epileptic events. Other physical alterations, such as change in head position, rolling in bed, looking up at a high shelf or

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bench, precipitating an attack would suggest a vestibular basis. Relationship to eating might establish a hypoglycaemic basis.

Events that occur from sleep, even if only some of the time, are almost always epileptiform. Sleep disorders enter the differential diagnosis. Non-epileptic seizures (NESs) never occur from sleep, although some patients maintain they were asleep when they occurred, and this can be hard to resolve without video-electroencephalography (VEEG) monitoring [4]. Seizures are sometimes linked to particular phases of the menstrual cycle, and whilst once interpreted as a functional element, this is very common in women with organic episodes and should always be taken seriously.

Episodes that occur when under emotional stress, if in difficult circumstances, particularly in the cognitively impaired, might relate to behavioural problems rather than seizure activity; however, the distinction is sometimes difficult, and this can be further complicated when it is suggested that the behavioural alterations are a feature of a postictal state.

The symptoms in the immediate moments prior to the event are diagnostically critical. Those who describe focal neurological symptoms, such as clonic jerks, olfactory or gustatory hallucinations, rising epigastric aura, intense déjà vu or similar phenomena, are likely to be experiencing seizures; however, some symptoms can be fairly non-specific, such as light-headedness and dizziness. True vertigo is rarely a feature of epileptic attacks but it is not always easy to distinguish vertigo from brief seizures. A visual aura can be epileptiform but more often is migrainous. If a typical account of shimmering scotomatous deficit evolving over some minutes with or without a headache following, and possibly associated with other neurological symptoms, is described then migraine becomes a strong possibility.

The duration of attacks is probably the best single guide when considering the nature of the episodes. Epileptic events are almost always seconds to minutes in duration. Migrainous neurological symptoms are usually 15–20 min in duration; the subsequent headache can last for hours but may occasionally be absent, and if so there is a much greater likelihood that they will be misdiagnosed as seizures. With epileptic events, there is often some warning and gradual build-up to maximal deficit whereas, with ischaemic vascular episodes, the onset is abrupt and typically maximal deficit at the outset with gradual resolution. Since consciousness is usually unimpaired in focal cerebrovascular events involving the hemispheres, altered consciousness during attacks of this type is more suggestive of an epileptic aetiology. Generalized tonic–clonic seizures typically last 40–90 s but occasionally longer. Reports of attacks lasting hours, whether considered to be complex partial events or generalized tonic–clonic attacks, should always raise the suspicion of non-epileptic episodes. Although status epilepticus, both convulsive and non-convulsive, can certainly be prolonged it is a relatively uncommon event among people with chronic seizures.

After an event, rapid recovery, perhaps with sweatiness or nausea and vomiting, is more typical of syncope than of epilepsy. Tonic–clonic seizures are almost always followed by a period of confusion. Occasionally there is marked alteration in mood and behaviour postictally; less often a true psychosis occurs postictally which, although typically self-limiting, sometimes dominates the presentation.

Activity during the event often helps clarify the nature of the attack. If absences are typical with abrupt cessation of activity and prompt resumption of activity at the end of the few-second-long episode then the diagnosis is usually clear. Classical complex partial seizures with a warning followed by loss of contact, oral and manual automatisms and postictal confusion, sometimes with lateralizing signs noted during or after the event, are obviously clear cut. Generalized convulsive activity can be more difficult to distinguish from syncope. Generalized tonic–clonic seizures may or may not be preceded by a warning; the event usually lasts less than a minute or two, lateral tongue biting and incontinence are common, the eyes are often noted to be open with the eyeballs rolled upwards and there is often marked confusion postictally. The total absence of confusion after a generalized convulsive event should immediately raise the suspicion that the event was not epileptic.

During a seizure, well-organized motor activity is uncommon, though automatisms can sometimes be preservative and simple activities are continued, although in an incomplete and sometimes clumsy manner. The purposeless nature of motor activity during the events usually draws the attention of those around the patient. The normal performance of complex activity, such as driving a car, or riding a bicycle, suggests that the attacks are non-epileptic. Partial seizures of temporal lobe origin are usually associated with altered consciousness, at least to some degree, though this is often not perceived by the patient. There are accounts of patients suffering generalized tonic–clonic convulsions and being able to recall events around them after the episode. When this occurs, it is usually because the motor activity is actually caused by partial seizures of frontal or parietal origin, when consciousness can sometimes be preserved despite the bilateral symmetry of the motor activity [5].

Similarly, seizures of extratemporal origin, particularly those originating in the frontal lobes, sometimes have bizarre features that may be similar to non-epileptic events. Furthermore, VEEG monitoring with scalp electrodes can be unremarkable during these events, obscuring the issue diagnostically. Helpful clues are the stereotypic nature of attacks, which often cluster, and that they may occur from sleep. If unusual events occur in association with a structural cerebral pathology, the diagnosis is usually clear. Great caution must be exercised diagnosing non-epileptic events in patients with bizarre clinical events that have a structural pathology demonstrated on MRI, particularly if it is extratemporal in location.

Prolonged ‘absences’, typically occurring during driving, are a common reason for referral to the epilepsy clinic. The patient describes driving or walking some distance, and then finding themselves at their destination (or just missing it), and not able to recall how they got there. If they have made the trip without difficulty, arrived at their destination and there is no sign of damage to the vehicle, it is highly unlikely such activity occurred during a seizure. These patients – and the referring doctors – are typically very anxious about the event (in contrast to many patients who have had complex partial seizures whilst driving!). It can be difficult to provide satisfactory reassurance that this is a benign phenomenon experienced to some degree by many people.

Neurological examination is rarely helpful in patients who present with episodic disorders. Stigmata of a phakomatosis, the

finding of a significant hemiatrophy, lateralized weakness or reflex change and, of course, transiently lateralizing signs immediately postictally can be very useful. Directly after a seizure, the most useful physical sign is perhaps the observation of petechiae over the upper trunk and face in particular, sometimes a quite striking phenomenon but usually subtle. Tongue bites and evidence of incontinence might be present if the patient is seen early enough. Although most tongue bites are lateral after epileptic seizures (lateral tongue biting is a highly characteristic feature of an epileptic seizure and rarely due to other causes), lacerations of the tip of the tongue and occasionally even the lips or cheeks can occur. Injuries such as fractures and bruising are not so helpful, often occurring through loss of consciousness with syncope for example. Shoulder dislocation, particularly posterior dislocation, and crush-fractured vertebrae are almost diagnostic of a seizure and are never seen in syncope or non-epileptic events. Back pain or radicular pain post event should always be investigated with radiography of the region; these injuries are often not diagnosed correctly and can lead to significant problems in returning to normal activity.

Tests for vestibular abnormalities might be performed and sometimes provoke attacks. Cardiac examination might disclose features to suggest an alternative aetiology for episodic disorders. Cardiac bruits, valvular heart disease, cardiomegaly or postural hypotension, tics and other movement abnormalities might be detected during the physical examination. Occasionally patients have seizures whilst being examined; most often, these episodes are non-epileptic. Hyperventilation might be induced deliberately having informed the patient of your purpose, but other floridly non-epileptic attacks are sometimes brought on by simple tests, such as deep tendon reflexes, fundoscopy or suggestion. Great caution must be exercised when interpreting such events, but most often they provide strong primary evidence as to the true nature of the episodes. Vulnerable patients with epilepsy may easily be induced to have non-epileptic events in some circumstances, particularly if they believe the organic nature of events is being questioned. There is considerable pressure to 'perform' for some, whether during the examination and history or VEEG monitoring. Thus, the use of suggestion and other provocative procedures should only be performed in special circumstances [6]. Procedures such as the injection of saline are deceitful and unethical.

Laboratory tests, such as biochemistry and haematological screens, add little to the diagnosis of epilepsy. Occasionally, a primary metabolic disturbance such as hyponatraemia is found but this almost always occurs in a specific clinical setting and in the context of other recognized metabolic abnormalities. Elevation in creatine kinase and white blood cell (WBC) count might transiently occur after a seizure [7]. Serum prolactin levels rise transiently after seizures, reaching a peak at about 15 min after the event and returning to normal after around an hour. Obtaining a blood prolactin level can be useful then in the diagnosis of events of uncertain type, provided it is done close enough to the episode. Prolactin levels are elevated following generalized convulsions in about 90% of cases, following complex partial seizures in probably only about 50% and not elevated following simple partial episodes. There is some uncertainty as to how prolactin changes might be interpreted in other settings, such as syncope and migraine. Elevations of similar order of magnitude have been found in vasovagal syncope as in seizures [8]. Also, numerous medications and other pathological conditions can cause changes in prolactin levels, although these generally do not cause transient fluctuations like seizures do [9,10]. Although in principle serum prolactin ought to be a useful test, it is difficult to implement because of the time scale and the fact that most seizures do not occur in circumstances where obtaining an acute sample is possible. At times, though, serum prolactin estimation provides useful supportive information. It is not appropriately used as the primary diagnostic modality [7].

Other tests that can be useful include structural imaging, CT or MRI. Visualization of a focal cerebral pathology involving the cortex may provide useful supportive evidence for a diagnosis of epilepsy, but finding a structural pathology does not prove attacks are epileptiform. Conversely, not finding a structural pathology does not exclude a diagnosis of epilepsy, even if the symptomatology is focal. The sensitivity of MR scans particularly with quantitative measure is now so great that it is uncommon in focal seizures of long standing not to find a relevant abnormality. However, in some patients abnormalities are never demonstrated, perhaps because they are too small or subtle or because it is not a focal syndrome. The aetiology of these seizure types is often unknown and many appear to have a relatively good prognosis.

Functional imaging tests such as single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) are more appropriately done in conjunction with VEEG monitoring or as part of surgical workup in specialty epilepsy units. They are rarely helpful as a diagnostic procedure.

Electroencephalograms (EEGs) and VEEG monitoring are extremely useful tests but need careful interpretation. Unfortunately EEGs show an enormous range of minor abnormalities, benign variants, artefactual change and other confusing features that are often misinterpreted as evidence that there is a cerebral disturbance of some sort [6,11–13]. Although EEG can provide confirmation of precisely the type of epilepsy, and occasionally the location of a structural pathology, more often it leads to erroneous diagnosis of epilepsy when minor changes are misinterpreted. The EEG should never be substituted for a good clinical history; EEG changes, even if epileptiform, should be interpreted cautiously. There is a very strong case to be made for not doing studies like EEG if the primary diagnosis is non-epileptic, provided there are strong clinical grounds for an alternative diagnosis. This is particularly true if the episode was unequivocally syncopal clinically, when minor EEG abnormalities may lead the otherwise confident clinician (and patient!) to less certainty. VEEG monitoring is as close to a gold standard as is available. Actually capturing events, witnessing directly the physical accompaniment of the attacks and observing the EEG changes that occur with this, often allows a specific diagnosis or the exclusion of epilepsy. However, simple partial events, extratemporal episodes, particularly from the frontal lobes even if associated with altered consciousness, are sometimes not associated with clear changes on the EEG. On the other hand, all most complex partial events and all generalized convulsions will show diagnostic EEG changes. The scalp EEG is very often normal in simple partial

seizures, particularly those involving sensorimotor cortex, even if the seizure activity is continuous.

Repeated observations over time also help make the correct diagnosis. Clinicians often feel obliged to arrive at the correct diagnosis immediately and at first consultation in episodes where alteration in consciousness has occurred, but when the diagnosis is unclear it is better to leave the diagnosis open. An erroneous diagnosis of epilepsy has serious implications for the patient. The concern with unexplained episodes of altered consciousness generally relates to safety, driving and perhaps in the work place, and these activities might need to be restricted if the nature of episodes is uncertain but this will depend on specific circumstances and the frequency of attacks and their character. Even if activities do need to be restricted to some degree, this is a much better precaution than the so-called 'therapeutic trial' of anticonvulsant that often gives rise to uncertain and confusing results, sometimes leading to the de facto diagnosis of epilepsy. Much more harm is done through the incorrect diagnosis of epilepsy than by keeping an open mind and reviewing the situation when more information is to hand, after implementing appropriate safety precautions.

Syncope

Syncope is defined as an abrupt but transient loss of consciousness, with loss of postural tone and followed by rapid recovery, due to sudden reduction of cerebral perfusion. It is common, can have serious cause, and is frequently complicated by injuries. It may be very disabling. The cost of syncope is extremely high, with patients seeing on average three physicians to reach a diagnosis, at an estimated cost of US$5000 per admission, and over US$20 000 to get to a definite diagnosis of syncope after admission [14]. Epidemiologically, syncope has many features in common with epilepsy. It appears often in late childhood and teenagers, with a second peak in the elderly. The lifetime incidence of syncope is 3–5% [15,16], with slightly more women affected than men. Because many do not present to physicians, the true incidence is likely to be much higher; some have estimated a 20–30% lifetime risk of a syncopal episode. It is more frequent in the elderly, with an annual incidence of 6% in those over 75 years old, who have a higher risk of injury. Neurocardiogenic (vasovagal) syncope is most common in early life; cardiac causes become more common later on. Whereas syncope due to cardiac disease is potentially life threatening, syncope as a result of other causes is generally benign [17]. The recurrence rate is at least 50% in those who present for evaluation.

There are a variety of causes of syncope (Table 4.1) but in over 25% of patients no cause can be identified [18,19]. There has been considerable interest in the syndrome of ictal arrhythmias, with a syncopal event complicating a subclinical epileptic discharge. Well reported in a relatively small number of cases, this situation is probably a rare cause of syncope. In patients studied with VEEG monitoring, it is rare to see symptomatic syncope complicating the frequently observed but usually minor disorders of cardiac rhythm that may occur during the ictus [20]. When this does occur, it is more likely in patients with temporal lobe foci. It may be the presenting feature of the seizure syndrome, and is thought to require cardiac pacing as well as anticonvulsant therapy if symptomatic [21–23].

Table 4.1 Causes of syncope.

Neurocardiogenic
Orthostatic hypotension
Arrhythmias
Other autonomic causes
Other cardiac causes
Psychiatric causes
Unknown cause (SUO)

SUO, syncope of unknown origin.

Any seizure that occurs in specific circumstances should be regarded with suspicion. These are sometimes erroneously diagnosed as 'reflex seizures'. An excellent example is the patient who arrives with a referral describing seizures that only occur during or immediately after venesection (often when having blood taken for anticonvulsant levels!). Episodes occurring during micturition, defecation, coughing or with Valsalva, whether during weightlifting or deliberate, should suggest a diagnosis of syncope [24]. Often the precipitant for a syncopal event is not obvious and the patient will reveal it only if specifically questioned. Male patients particularly may be embarrassed to disclose painful or emotional precipitants, especially if they perceive that the circumstances are relatively minor. Good examples of this include syncopal events occurring in cinemas during violent or bloody scenes, during venepuncture, or watching minor surgical procedures. Even visiting hospitals, discussing medical procedures, reading an unpleasant book or reminiscing on a painful or unpleasant experience can be sufficient stimuli. The last example particularly applies to children, and events that have occurred under these circumstances should be considered syncopal until proven otherwise [25]. It is of course more obvious if the patient is undergoing a surgical procedure, or has seizures in the setting of some acute medical illness, but it is surprising how often epilepsy is misdiagnosed under such circumstances. Syncopal events related to primary cardiac disease less often have a well-defined aura than syncope due to neurocardiogenic episodes [26–28]. Cardiogenic syncope leads to sudden collapse and usually lacks situational precipitants.

In the lead-up to syncope, the patient has sometimes been unwell, sleep deprived or is 'run down'. It may be in the cooling down period after vigorous exercise, with a combination of vasodilatation and erect immobility, resulting in transient hypotension. At home, events are often in the kitchen, when prolonged standing is common, or in the bathroom, again associated with standing immobile for long periods but also with micturition or defecation. Standing in a hot shower, in supermarket queues and waiting for tickets, standing at church or at assembly are also common situations. They may be in a crowded warm environment such as a cinema or club. Alcohol has often been consumed, and this is frequently associated with a late night. The patient is often standing at the onset of the event, but syncope may occur while seated although rarely while recumbent. In the latter situation there is often some specific precipitant (i.e. pain). Familial

predisposition to syncope is common, and migraine frequently co-exists in these patients [29].

At the onset of the event frequent symptoms are nausea, often with a rising quality, light-headedness and sweating. There is often the urge to get outside into cool air. Anxiety and claustrophobia may dominate the account. Patients often describe 'I knew I had to get out' or 'I had to get some air quickly'. Anxiety is often marked at this point, leading the episodes to be confused with panic attacks. Witnesses may observe pallor and sweating, and may report the subject to be confused or semiresponsive. The event may progress no further than this, so-called 'presyncope', or go on to a more typical event with collapse. Immediately prior to loss of consciousness symptoms such as an auditory disturbance with noises 'sounding distant' or 'as if from down a tunnel' are frequently reported, then flaccid collapse. More complex auditory and visual hallucinations are surprisingly common, seen in 36% and 60% respectively of Lempert's series [26]. Visual hallucinations are sometimes quite complex, and may involve figures and scenes, and be associated with familiarity or even déjà vu [28,30,31]. 'Out of body' experiences have been described [26]. Auditory hallucinations are usually of ringing or roaring, sometimes voices are described though, and, as with partial seizures, these often have a familiar but unidentifiable quality about them.

Generalized stiffening and then clonic limb movements are frequently described by witnesses. The limb movements are usually asynchronous but multifocal, and sometimes seen to involve one limb or side asymmetrically, rarely exclusively. Facial involvement with the myoclonic limb movement is common. Head turning is rarely seen, but that and asymmetric dystonic limb posturing are certainly recognized. Estimates of the frequency of tonic and clonic components range from 40% to 90%, and depend on the quality of the witnessed account [32,33]. Medical or paramedical personnel are perhaps most prone to confuse the events with epileptic convulsions, testimony to the often dramatic nature of the convulsive activity. Eyes are usually open during the event, and sometimes oral and perseverative manual automatisms can occur. Automatisms of this type may be seen in the presyncopal phase also [27]. Head turning is a feature more often seen with seizures, but can be seen in syncope, as can dystonic posturing of the upper limbs, which may be asymmetric. Salivation may be noted also [34].

Typically, the duration of the convulsive activity is less than 15–20 s but, rarely, prolonged convulsive activity may be provoked. This is more likely if the subject is held upright during the event, usually by well-meaning bystanders, or if there is an underlying cause that persists. Urinary incontinence is not uncommon in syncope, a fact surprisingly little known among physicians. Respiration is seen to briefly cease in some instances. On recovery the patient is usually quite lucid, and in the elderly confusion postictally can be marked with syncope. Patients often report feeling 'washed out', occasionally for prolonged periods after the event, and will often prefer to sleep. Tongue biting is seen very rarely, perhaps when a hypoxic seizure has complicated syncope, but can certainly occur. Shoulder dislocation and bony injuries are rare. Lateralized neurological signs should not be seen in the postictal phase. Vomiting and marked diaphoresis are often reported in the postictal phase and the patient often appears grey and unwell. Cyanosis is rare, in contrast with epileptic events [24]. The marked confusion and drowsiness that follow epileptic convulsions are not usually confused with these features, but sometimes it is a difficult distinction, particularly if the patient sustained a significant blow to the head during the episodes. Syncopal episodes often occur in clusters, sometimes one after another, frequently as the patient is helped up from the first collapse. Where the sitting position is forced through restraint, such as with a car seatbelt, quite prolonged reflex anoxic seizures sometimes occur. A similar situation may be observed after cardiopulmonary arrest, when delayed seizures may be pronged and recurrent.

Examination is typically unrewarding; patients usually have normal resting blood pressure and appropriate postural responses between episodes. Even if measured immediately after the event, no abnormality is the rule, although contributing factors should be looked for including a primary arrhythmia, hypotension, inappropriate bradycardia and carotid sinus hypersensitivity. Fall-related injuries may be noted, usually in the form of facial trauma. Elevated creatine kinase levels, although more typical of a generalized convulsion, may be seen with syncope (even after those with trauma are excluded), although typically levels are much higher [35]. Elevated CK-MB levels have also been reported in syncope [36].

Features of syncope that should alert the clinician to the possibility of a serious underlying cardiac condition include a history of coronary artery disease or congestive cardiac failure, precipitation by exercise, palpitations at the onset or the occurrence of the events at the peak of exertion, an abnormal ECG, family history of sudden death and breathlessness with the episodes. Scoring systems to define those at higher risk in the emergency department have been devised [37].

If the history is typical, extensive investigation should generally be avoided in patients with syncope. However, if there is diagnostic uncertainty, or if the events are frequent, cause anxiety, limiting activity, or if a cardiac arrhythmia is suspected then investigations are appropriate. If the event can be induced by reproducible stimulus (i.e. venepuncture or pain) then it may be practical to induce an event when under electroencephalography or electroencephalography monitoring in order to document the typical features of neurocardiogenic syncope with ictal bradycardia or asystole associated with profound slowing of EEG patterns. Routine ECG tracing, echocardiography and chest radiography may be indicated. Because events are rarely frequent enough for spontaneous episodes to be recorded during inpatient monitoring, ambulatory studies with Holter monitoring, or more recently implantable loop recorders, may be more appropriate. Loop recording can be done for periods of up to 18 months, and is clearly the investigation of choice in many of these patients. A recent study demonstrated a surprisingly high rate of primary cardiac arrhythmias in patients misdiagnosed as suffering from refractory epilepsy [38].

Tilt table testing has been available for some time but its use remains controversial, particularly in relation to provocative drugs used to increase the sensitivity of the test, and interpretation of the results. Although this is a valuable adjunct to diagnosis in many patients, the wide range in results between centres should be recognized [39]. Carotid sinus massage may be helpful in the diagnosis, but this finding has low specificity in the elderly

population where it is most often found. Cerebral imaging may be useful in some cases, and finding a cerebral cortical pathology suggesting an epileptic basis will be helpful in management of a patient with refractory syncope.

Treatment of syncope depends on the cause. If a clear cardiac cause is demonstrated, specific therapy is obviously indicated. Most people, however, have neurocardiogenic syncope, and their treatment consists primarily of reassurance and avoidance of precipitating circumstances. When typical premonitory symptoms are recognized, preventative measures should be promptly undertaken. Usually this consists of lying or sitting with the head between the knees, and rising cautiously and slowly after the episode seems to have abated. Attention to hydration is an important element in many, as may be avoiding alcohol. Other drugs, such as antihypertensives, may require adjustment. The patient should be counselled about other agents that may provoke or precipitate syncope: alcohol, calcium channel blockers, ACE inhibitors, beta-blockers, barbiturates, prazosin, diuretics and sildenafil citrate are some of the more frequent offenders. Other conservative measures include increasing salt consumption and 'tilt training' [40], although the role of the latter is uncertain [41]. Isometric exercises of the upper limbs (squeezing a ball such as a darning ball, leg crossing) are often utilized, and have been shown to be effective in neurocardiogenic syncope [42].

Therapeutic data from large randomized controlled trails relating to neurocardiogenic syncope are very limited [43]. Evidence for the use of lipophilic beta-blockers remains controversial, but the recent prevention of syncope trial (POST) study did not find evidence of efficacy for metoprolol [44]. Serotonin reuptake inhibitors [45], ACE inhibitors [46] and midodrine [47] are the only agents that have been shown to be effective in randomized controlled trials. A large RCT with fludrocortisone is currently in progress [48]. Elastic stockings, with or without fludrocortisone, are used widely but, like disopyramide, have not been shown to be effective. Cardiac pacing had been shown effective in two randomized controlled trials [49] for the treatment of refractory neurocardiogenic syncope, but is now felt perhaps to represent the non-blinded nature of these studies and a reflection of expectation rather than real benefit [50].

Post-concussive events [51], in which tonic posturing, clonic movements or confusion stares are seen shortly after a concussive injury, are felt by some to represent a syncopal event, although there is some evidence to suggest such injuries have an epileptic basis. Either way, the prognosis is excellent and recognition of this distinctive syndrome important, particularly in the emergency department setting.

Non-epileptic seizures

Non-epileptic seizures (NESs) has become the preferred term to describe the events referred to often as pseudoseizures, psychogenic seizures or hysterical seizures, as it lacks the pejorative implications of the older names. Definition of these episodes is difficult; convulsive activity is witnessed but has no electrical correlate and is felt to reflect psychological stresses of some sort, though these are rarely specifically identified [52]. These episodes may be extremely difficult to distinguish from epileptic events, even by experienced observers. As a result, one of the most useful applications of VEEG monitoring has been to recognize and clarify these events. Although in some series up to 40% of patients with refractory seizures have NES, a more realistic proportion is 5–10% [6,11,12,52–54]. Patients with NES consume a disproportionate amount of resources at epilepsy centres – the patients present frequently and dramatically, often have inpatient stays and seek more consultations with neurologists. They typically consume more medications than those with organic seizures alone. Often they receive health benefits of some sort, are unemployed and require high levels of care at home [52].

There is no consensus on the mechanism of these events from a psychiatric point of view, and often no specific psychiatric diagnosis can be made; the disorder itself seems to be the sole clinical manifestation of the problem [55]. Recent work has suggested the events are best considered as a manifestation of a personality disorder [56]. Munchausen's syndrome by proxy, in which the description of seizures in the child is fabricated by the caretaker, is a form of child abuse and represents a different situation [57].

The clinical features of NES vary enormously. Although it is often precipitated by emotional stress or specific circumstance, this is not always the case. There is sometimes a family history of epilepsy, of epilepsy earlier in life or of personal encounters with epileptics, perhaps in a paramedical situation or as a carer. Events are usually very disruptive and dramatic, typically leading to multiple hospital admissions, and have a propensity to occur in public where they may be readily observed. Although there are many reports of a high rate of co-existence of NES and epilepsy, this is in fact a very uncommon occurrence [11].

The events themselves may consist of loss of contact, flaccid collapse and immobility or florid motor activity, often with side-to-side head shaking, pelvic thrusting and back arching. Variability from one event to another is common, making the lack of stereotypy a valuable clinical feature. The prolonged duration of many of the episodes is the most obvious clue to their non-organic nature. It is not uncommon for episodes to wax and wane from 30 min to hours in duration. Crying and screaming may be striking features of the episodes, and complex organized activity may be seen. Eyes are usually held closed during the episodes. Cyanosis is infrequent, but can be seen in some patients who may have what appears to be an adult version of breath-holding attacks. Tongue biting and urinary incontinence are sometimes reported (but rarely confirmed), although mainly by patients with a long history of this disorder. Interestingly, almost exclusively this group of patients reports fecal incontinence. After the event recovery is usually rapid and often accompanied by emotional distress. However, not all events resolve rapidly, and prolonged unresponsiveness with normal vital signs may follow. The lack of tachycardia during this phase is a helpful feature diagnostically but may be complicated by the sometimes frenetic motor activity of the episode. This may cause elevated creatinine kinase levels on testing, helping to reinforce the organic basis of the episode to emergency department staff and intensivists, who frequently deal acutely with such patients.

Typically, many anticonvulsant medications have been prescribed without benefit. Furthermore, some patients have been treated urgently with parenteral benzodiazepines or even paraly-

sis and intubation in a critical care setting. In many centres, NES is the most common cause of uncontrolled seizures in the intensive care environment and should always be considered as the diagnosis when a patient with chronic seizures presents in status without obvious cause.

Some non-epileptic events are embellished organic syndromes, such as syncope or hyperventilation. The clinical scenario occurs in a hysterical or anxious person who experiences syncopal symptoms, hyperventilates and then evolves into a very complex and clearly non-organic behaviour that attracts attention while the prodrome becomes lost in the drama.

Confirming the diagnosis may be a challenge unless monitoring (VEEG) is utilized. Patients who refuse monitoring, or those who have no events while being monitored, present a very difficult diagnostic problem, but most will have typical events in hospital. Often they can be encouraged by suggestion to produce episodes. Some centres have used other provocative manoeuvres, such as saline injection, but this may make interpretation of the events more difficult because there is considerable pressure on the patient to 'perform' and typical attacks may not be evoked [38,58]. As part of the illness involves the drama and frequency of the seizures, usually outpatient VEEG monitoring will be sufficient to make the diagnosis [53,58].

Epileptic seizures that are commonly mistaken for NES are frontal lobe seizures and simple partial seizures. Seizures originating in the frontal lobe can be bizarre, frequent, and associated with preserved awareness, and they are often refractory to medication. The stereotypic nature of the events, many of which may occur from sleep, and usually some response to acute parenteral therapy provide clues. However, VEEG may not demonstrate significant change during these episodes and movement artefact frequently obscures interpretation.

A diagnosis of simple partial seizures may be difficult to be certain about as the seizures are often not accompanied by scalp electroencephalography changes. In these situations the finding of a relevant structural abnormality on imaging studies supports the diagnosis of seizures, but negative imaging studies do not exclude it.

Management of NES is complex and difficult [52,55,56,59]. Engaging the patient in a therapeutic relationship is the most valuable component, followed by an explanation of the non-electrical basis of the events and recognizing that the condition causes disability. Confirming this belief with the patient takes much of the tension out of the situation. Confronting patients with a diagnosis of functional illness does little for their long-term care and often leads to re-presentation to other hospitals, with the consequent risk of inappropriate therapy. A face-saving compromise is often required, with an agreement by the patient to reduce or withdraw anticonvulsant therapy, avoid hospitalization and, where appropriate, to seek help from a psychiatrist to address underlying issues, such as depression. Accepting the care of one neurologist, or at least of one centre, is a major component of the clinical management plan [56]. However, controversy exists as to whether these patients should be managed by neurologists at all (in my view psychiatrists have little to offer these patients) and the temptation to treat with anticonvulsants is too great in the primary care setting. Engaging the patient in a positive therapeutic relationship minimizes risk, enables the anticonvulsant medications to be managed appropriately, and can lead to a good long-term outcome.

Panic disorder

Panic attacks can appear very similar to seizures They are episodes of fear or discomfort that are often accompanied by somatic symptoms such, as palpitations, dizziness, light-headedness and epigastric sensation, which may have a rising element [60,61]. The attacks have an abrupt onset, typically reaching a peak within 10 min. Hyperventilation is often prominent. Fearful patients want to escape and feel that the episodes indicate a life-threatening disorder. The attacks can be situational but most often occur spontaneously without a clear precipitant. As with seizures, attacks can be nocturnal and can cluster, occurring many times daily after long breaks between episodes. Overlap with the symptomatology of both complex partial seizures and syncope is marked, and seizures are not infrequently initially misdiagnosed as panic attacks, rather than the reverse [62].

Lifetime prevalence has been estimated at around 2%, with a higher risk for women. There is a significant familial incidence. Although the condition is usually diagnosed in young adults, it has been described in children and the elderly. Highly variable in severity, these episodes are often disruptive and overlap considerably with other psychiatric syndromes, particularly agoraphobia and depression. At least 50% of patients with panic disorder develop a significant depressive illness during their life; the majority are depressed when they present for treatment [63].

Management consists of a reassurance directed at specific unfounded concerns regarding underlying illnesses and psychiatric therapy of the phobic and depressive elements [63].

Migraine

Migraine is surprisingly often mistaken for epilepsy, particularly when the headache is mild or absent [64]. Migrainous aura may have visual, sensory or motor features that are suggestive of seizure activity and alertness is sometimes impaired. Postictal headache is common in epilepsy and often has a vascular quality, which may further complicate the diagnosis. Migraine and epilepsy may share a common pathophysiological basis [65].

Some unusual types of seizures, particularly those that originate in the occipital lobe, can be difficult to distinguish from migraines because features such as visual disturbance occur in both disorders [66,67]. Because there is no diagnostic test for migraine, the diagnosis is clinical. Migraines are more common among those who suffer syncope and there is often some overlap with the symptoms. Although visual disturbances are the most common neurological feature of migraine, sensory or motor change, speech disturbance, amnesia or confusion and even loss of consciousness may occur.

Migraine may have specific triggers, such as foods, medication, emotional stress or visual stimuli. Sensory or visual symptoms generally build up slowly and typically spread over minutes, progressing stepwise from one affected cortical region to the next, with resolution of the symptoms occurring as each new region

becomes involved. Typical symptom duration is 15–30 min, although occasionally episodes last longer and may not be followed by headache.

As epilepsy and migraine are both common, one might anticipate encountering them occasionally in the same patient. This has been studied by a number of authors [68] with differing results. There seems to be no excess of epilepsy among patients with migraine overall [69]. Marks and Ehrenberg [70] showed 20% of 395 patients with epilepsy had migraine, and 3% had migrainous phenomena immediately preceding seizures, for which they coined the term 'migralepsy' [71]. They also noted that there seemed to be a particular link between catamenial epilepsy and migraine with aura. Some authors have postulated that migraines might be a seizure equivalent [72].

Postictal migraine is well recognized and may have some lateralizing value [69,73]. Seen in focal and generalized syndromes, it more often occurs after a tonic–clonic convulsion. Ito *et al.* [74] showed that migraine-type headaches were more common in those with occipital and temporal epilepsies than in events of frontal lobe origin [74]. The increased cerebral blood flow that is induced by seizure activity is felt to be responsible for this headache. Often these types of headaches occur in patients who suffer migraines at other times. However, the patient who presents with new-onset headache and seizure obviously requires the exclusion of an acute neurological problem, such as intracranial haemorrhage or infection.

Seizures of occipital origin have many features of migraine, with visual hallucinations or amaurosis often complicated by headache. Benign partial epilepsy with occipital paroxysms is a syndrome of childhood to teenage years [75,76]. Hallucinations are typically simple in nature but can be complex and followed by complex partial or generalized convulsions [77], after which come the headache with nausea and vomiting. The diagnosis depends on observing the distinctive interictal EEG pattern. Occipital seizures resulting from structural pathologies, such as coeliac disease and mitochondrial encephalomyelopathies, may share these features [78].

Non-specific EEG changes occur with migraine, but specific epileptiform abnormalities are rare [75]. Finding interictal spikes in patients with migraine suggests an alternative diagnosis, such as benign occipital epilepsy in children or the possibility of a structural lesion in adults. As a rule, electroencephalography is not useful in typical migraine. Minor abnormalities seen during episodes need to be interpreted with great caution.

The diagnosis of migraine is clinical and rests on recognizing the typical progression of symptoms, the duration of attack (tens of minutes rather than seconds), and gradual resolution. Response to anticonvulsant therapy is an unreliable basis for making the diagnosis.

Sleep disorders

A review of the many abnormalities that arise from sleep is outside the scope of this brief chapter. However, sleep disorders, such as periodic limb movements of sleep, rapid eye movement (REM) sleep disorders, narcolepsy and cataplexy, can be confused with seizures [79,80]. On the other hand, some epilepsies arise exclusively from sleep and there is a propensity for partial seizures to occur in sleep or shortly after waking [81]. Benign rolandic epilepsy is an example of a seizure syndrome that is associated with sleep.

The parasomnias, including sleep walking, night terrors, restless legs, nocturnal myoclonus, bruxism and REM sleep disorder, can be more difficult to differentiate from seizures [82], whereas disorders with hypersomnolence rarely present diagnostic problems. Sleep disorders are common, particularly in the elderly. Obstructive sleep apnoea has been recognized to precipitate seizures in the elderly with epilepsy [83], and REM sleep disorders have been recognized to be more common in patients with epilepsy, perhaps because of a shared pathological substrate, thus often causing diagnostic confusion [84].

Although the classic tetrad of narcolepsy involves excessive daytime sleepiness, cataplexy, hypnogogic or hypnopompic hallucinations and sleep paralysis, not every component occurs in a given individual. The diagnosis is based on sleep latency studies in which REM sleep begins abnormally early. Cataplexy, sudden episodes of sleep, and hallucinations are sometimes misidentified as seizures [85]. Rarely, cataplexy precipitated by laughter is mistaken for a gelastic seizure.

Paroxysmal nocturnal dystonia presents as an often dramatic movement disorder from sleep. Typically, there is arousal and then vigorous motor activity. Episodes typically last 30–60 s, followed quickly by sleep [86]. There is amnesia for the episodes. Many patients originally diagnosed with this condition have since been recognized to have frontal lobe epilepsies [80,87]. The diagnosis is made all the more difficult by movement artefact obscuring EEG traces made during the episodes. Video, without electroencephalography, is often helpful in differentiating the two conditions. The history of daytime seizures is also helpful in confirming a diagnosis of epilepsy.

Night terrors (*pavor nocturnus*) are a childhood parasomnia. Children wake from sleep screaming and crying inconsolably for many minutes, after which they go back to sleep and are amnesic of the episode. Autonomic features may be prominent and there are sometimes vocalizations. Events usually occur from slow wave sleep, typically 30 min to 4 h after going to sleep. Rarely, night terrors persist into adult life. If the diagnosis is in doubt, ictal EEG recordings can confirm that these do not have an epileptic basis [88,89]. Sleepwalking is a related problem, and the features are well known to the general population [90]. The automatic activity of wandering is sometimes less florid, featuring motor activity that may imitate the automatisms of complex partial seizures, with repetitive hand movements.

Bruxism, or tooth grinding, can be a very striking nocturnal phenomenon. It is a benign disorder that requires no specific therapy. Hypnogogic myoclonus, although a normal event most have had experience of, sometimes brings patients to the epilepsy clinic, often through the observations of an anxious partner and sometimes in the setting of recognized epilepsy. Pathological fragmentary myoclonus, in which fragments of myoclonus of early stage sleep persist into stages 3 and 4, may be seen with any cause of disrupted sleep.

Periodic movements of sleep are so distinctive that it is rare for them to be confused with seizures [91]. They are characterized by repetitive flexion and extension, sometimes quite vigorously,

of hip, knee, ankle and toe for a period of 30 s or so. The episodes frequently recur throughout the night, troubling the bed partner but not the patient.

The REM behaviour disorders are much more complicated. These episodes occur from REM sleep and consist of the individual acting out components of dreams. Sometimes dramatic and prolonged, the activity can be complex, violent or aggressive and accompanied by agitation and vocalizations. Typically recurrent, the attacks present a risk of injury for the partner. Causes include structural brain injury, such as subarachnoid haemorrhage. In some situations REM behaviour disorder might be difficult to distinguish from postictal confusion [88].

Although most parasomnias can be distinguished from epileptic disorders by their distinctive clinical features, polysomnography allows definitive diagnosis in most instances [92].

Vertigo

Vertigo with brief episodes of dysequilibrium is often misinterpreted as seizure activity, at least by referring physicians. This is because many patients describe the episode as involving loss of awareness, although this is not confirmed by witnesses. Although vertigo may rarely occur as a feature of focal seizures, especially those originating in frontal or parietal regions [93,94], other non-specific symptoms, such as light-headedness and dizziness, are more often reported as a feature of convulsive episodes.

In vertigo caused by peripheral vestibular causes, the episodes are often provoked by head movement, as in benign positional vertigo, and are associated with nausea and vomiting. Sometimes eye signs can be seen during the attacks. Although witnesses typically observe consciousness to be preserved during episodes of vertigo, it is not uncommon for patients to report the sensation of loss of awareness briefly during a severe brief vertiginous episode. In so far as attacks sometimes lead to falls, they imitate epilepsy. Careful history, provocative manoeuvres such as the Hallpike test and, sometimes, vestibular testing may be required to make the diagnosis. True vertigo is a very uncommon feature of epileptic seizures.

Movement disorders

A number of movement disorders can imitate epilepsy. Paroxysmal choreoarthetosis or dystonia, both kinesogenic and non-kinesogenic forms [95], are movement abnormalities with striking posturing or chorea that are precipitated by sudden movement, surprise or startle, stress or rapid movement. Some forms are aggravated by alcohol, caffeine and fatigue. These are often unilateral and consciousness is preserved during the attacks. The episodes are often mistaken for focal motor seizures and the description of hemitonic seizures with preserved consciousness should raise the possibility of a paroxysmal dyskinesia. Similar symptoms might be secondary to demyelinating disease or other primary cerebral pathologies. The so-called tonic seizures of multiple sclerosis may be unilateral or bilateral and are sometimes precipitated by movement. Occasionally these entail what is interpreted as clonic movements, particularly as the attacks resolve [96]. Inability to speak during the episode may be interpreted by witnesses as altered awareness. The abrupt onset and extent of the attacks, as well as the lack of focal onset and typical rhythmic activity at the onset, are clues as to the true nature of the episodes. However, seizures, particularly those of frontal lobe origin, occasionally can cause abrupt tonic posturing.

Epileptic seizures precipitated by startle (startle seizures) often take the form of asymmetric posturing and collapse. These occur usually in epilepsy of frontal lobe origin. Sensitivity to startle often occurs in late childhood and recedes in later life. The episodes usually occur in cognitively impaired patients [97]. Often a hemiparesis is present, and other seizure types occur. The startle attacks might progress to more obvious convulsive seizure activity. Startle seizures can be mistaken for non-organic events and for paroxysmal dyskinesias. Hyperekplexia is a rare disorder of infancy, where an exaggerated startle response occurs in response to unexpected stimuli, particularly auditory events. After the initial startle, with exaggerated blinking and generalized stiffening, there may be vigorous limb jerks and head extension. Hypertonicity is often noted on handling of these infants. A variety of other features have been described, including periodic limb movements in sleep. The condition gradually improves. The condition spontaneously remits in the first years of life. Autosomal dominant and recessive forms of the disease have been described and a variety of genes have been associated with the condition.

Cerebral ischaemia

Vascular disturbances typically produce an abrupt onset of negative motor and/or sensory phenomena, speech disturbance or visual abnormality without alternation of consciousness. When this occurs in an elderly person at risk for cerebrovascular disease, the diagnosis is usually clear. Recurrent episodes of limb weakness, speech disturbance or paraesthesia in a limb have much in common with focal seizures. Ischaemic attacks tend to be maximal at the onset, last for a period of seconds to minutes, do not affect consciousness, and do not progress to more typical seizure activity. Neuroimaging, including echocardiography and carotid Doppler or angiographic studies, might allow a definitive diagnosis. Clonic jerking of the limb has been reported with transient ischaemic episodes and there may be some overlap here with seizure activity occasionally resulting from cortical ischaemia [98]. In general, the differentiation of cerebral ischaemia from seizure activity is straightforward. However, the most frequent seizures in the elderly are complex partial and thus can be missed by the unwary evaluator.

Endocrine and metabolic abnormalities

Disturbances of hormones, glucose, fluids and electrolytes can cause seizures or seizure-like events [99]. When occult abnormalities such as insulinomas present with seizures, the diagnosis can be challenging. The most common cause of transiently altered awareness due to endocrine abnormality is hypoglycaemia related to insulin therapy of diabetes. This can cause confusional episodes, generalized tonic–clonic convulsions and sometimes

episodes imitating focal seizures. Although hypoglycaemia is common, it usually presents to the primary treating doctor rather than to a neurologist.

Hypoglycaemic episodes can be mistaken for vasovagal syncope or seizures. Other than insulin therapy, causes of hypoglycaemia include alcohol, insulin-producing tumours, rare inborn metabolic abnormalities, such as the congenital deficiencies of gluconeogenic enzymes, and renal or hepatic disease [100,101]. Reactive hypoglycaemia may occur postprandially, or in association with other enzyme abnormalities, such as hereditary fructose intolerance.

The symptoms of hypoglycaemia include altered vision, diaphoresis, confusion, coma and altered behaviour in addition to partial and generalized seizures. Perioral and peripheral paraesthesiae, dysarthria, ataxia, tremor and palpitations are common features. Occasionally, true vertigo occurs. Some patients describe the symptoms as 'anxiety', or in otherwise non-specific terms. There is usually a prodromal period with prominent hunger. The behavioural change can be extremely bizarre, and hypoglycaemia should be considered in any patient with periods of unusual or prolonged episodes.

The relationship of symptoms to eating or fasting provides clues about the cause. The diagnosis is confirmed by measurement of serum glucose at the time of the event. Sometimes the rate of change of serum glucose levels is more important than the absolute glucose level. Hyperglycaemia can cause seizure-like activity and focal seizures are well described as features of hyperglycaemic states [102], sometimes in association with other neurological symptoms, such as movement disorders or lateralized weakness [103]. Hypocalcaemia can produce paraesthesia, carpopedal spasm, laryngeal stridor or convulsions [104]. Consciousness is preserved unless a generalized tonic–clonic seizure occurs. Hypocalcaemic sensory disturbances are sometimes misinterpreted as an aura.

Seizures rarely complicate a number of other endocrine abnormalities, including hypocalcaemia, hypo- and hyperthyroidism, generally only when the disorders are extreme. Phaeochromocytoma and other catacholamine-producing tumours can produce paroxysmal symptoms that might be mistaken for presyncope, anxiety or seizures. Flushing and palpitations due to phaeochromocytoma usually last longer than the autonomic features of seizures. Menopausal symptoms, such as hot flushes and paroxysmal sweating, are sometimes misinterpreted as seizure related. Seizures might be aggravated by hormonal change, such as those who suffer seizures in relation to the menstrual cycle, but again this is generally fairly clear [105].

Transient global amnesia

Transient global amnesia is an illness of uncertain aetiology. Some authorities feel it represents cerebrovascular disease, others attribute it to migraine and still others regard it as an epileptiform phenomenon [106]. Most would agree, however, that it is not an epileptic event. These stereotypic events are quite characteristic and easily recognized by the experienced clinician [107]. Amnesic episodes are recurrent in 8% of these patients.

The patient typically presents in a confused state, unsure of what they are doing or where they are going. Although they have little awareness of their current circumstances, they typically retain personal information. The episodes can last up to hours, after which small islands of memory start to return of what went on during the amnesic period. However, some never recover any memory for the time that was involved. As a result, these episodes typically cause great anxiety to those around them.

Although slightly perplexed or agitated during the attacks, no focal neurological abnormalities are found. EEGs and structural imaging are normal and blood tests provide no clues. However, the description of events is so characteristic that the diagnosis is generally straightforward. Most patients have a history of migraine and sometimes the episodes are followed by headache [108]. Rare causes include lacunar strokes.

The condition can be confused with the confusion after a generalized tonic–clonic seizure in cases where the seizure was not noticed. However, postictal confusion is generally global and lacks the peculiar specificity of the true transient global amnesic attack [109]. Patients with transient global amnesia need no further investigation and no other specific therapy besides strong reassurance.

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5 Mechanisms of Epileptogenesis

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Over a century and a half ago, Hughlings Jackson [1] defined epileptic seizures as 'an occasional, sudden and excessive discharge of grey matter'. This statement can be viewed as the culmination of a series of previous studies of animal electricity started by Luigi Galvani [2] and von Humbolt [3], and subsequently pursued using cortical stimulation experiments by Fritsch and Hitzig [4] and the clinical observations of Todd [5]. The scientific quality and prescient ideas of Jackson's work, however, mark the beginnings of the modern era of epileptology. Since then, increasingly refined investigatory techniques have provided a great deal of information about how epileptic discharges are generated and propagated within the central nervous system, and the many different ways in which they manifest themselves that we have learned to recognize from clinical observation. David Prince coined the term of 'epileptogenesis' [6] to describe the various pathogenetic mechanisms of epilepsy. Subsequently, owing to the emphasis given to the progressive course of some of these mechanisms, the term epileptogenesis has often been employed to define the process whereby an initial event leads to the constitution of a persistent epileptic condition. This section is devoted to the important concept of epileptogenesis as a process and the term *epileptogenesis* will be used in Prince's original context, irrespective of whether the mechanisms that we are referring to are the result of a progressive process or not.

As in the case of many other pathological conditions, experimental models made a major contribution to our understanding of epileptogenesis. The term 'experimental models' should be restricted to animals presenting spontaneous or experimentally induced epileptic seizures, whereas *in vitro* or computer models are more properly called models of epileptogenic mechanisms. This is not just a question of semantics, because the relevance of experimental results to the advances made in our understanding of epilepsy depends on how suitably the experiment has been designed for this purpose. Operationally, it is enough to say that an experimental preparation should be referred to as a model (of epilepsy, seizures, or epileptogenic mechanisms) only if it has been demonstrated that it faithfully reproduces the clinical and electroencephalographic characteristics of human epilepsies or seizures, or the biological changes that are known to be associated with them. Over the last few years, animal experiments have been effectively supplemented by human tissue studies of brain specimens surgically removed for the treatment of drug-refractory epilepsies. Experimental studies have shown that a number of different agents that affect excitatory or inhibitory neurotransmission, intrinsic cell excitation mechanisms or the ionic microenvironment can induce seizures.

A key to the investigation of cellular epileptogenic mechanisms came from studies of Matsumoto and Ajmone Marsan [7] (who were among the first to observe them in penicillin cortical foci). They showed that neurones belonging to an epileptic neuronal aggregate consistently discharged in the form of particularly protracted 'bursts' (Fig. 5.1), which are referred to as paroxysmal depolarization shifts (PDS). In a normal brain, this phasic type of cell discharge can also be seen in some 'intrinsically bursting' (IB) cell subpopulations of the neocortex and in area 3 of Ammon's horn (CA_3) in the hippocampus: both are particularly involved in synchronizing cortical activity. In both experimental epileptogenic foci and epileptic human tissue, spontaneous or stimulus-evoked PDSs have been found to occur commonly in physiologically nonbursting neurones, and can therefore be considered reliable hallmarks of an active epileptogenic process [6].

Epileptogenic procedures, such as the blockade of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission by bicuculline, picrotoxin and penicillin or the potentiation of excitatory amino acid (EAA)-mediated transmission by the kainate, ibotenate or *N*-methyl-D-aspartate (NMDA)-selective agonists, are all capable of inducing generalized phasic PDS-like activity in cortical cells. Similar effects can also be obtained by means of epileptogenic agents acting on the intrinsic mechanisms responsible for membrane excitability, such as Na^+ or Ca^{2+} depolarizing current activators [veratridine or ethylene glycol tetraacetic acid (EGTA) and 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,-*N*′,*N*′-tetra-acetic acid (BAPTA)] or the inhibitors of hyperpolarizing K^+ currents (tetraethylammonium, intracellular Cs^{2+}, 4-aminopyridine).

In this chapter, particular attention will be given to the epileptogenic mechanisms that putatively account for naturally occurring animal and human epilepsies.

Membrane ion channels

The excitability of nerve cells depends on the movement of ions through specific voltage-dependent or receptor-activated membrane channels. The kinetics of transmembrane ion currents has been extensively investigated by means of various types of voltage-clamp recordings, whereas the effects of ion currents on cell membrane potential can be detected by means of current clamp recordings.

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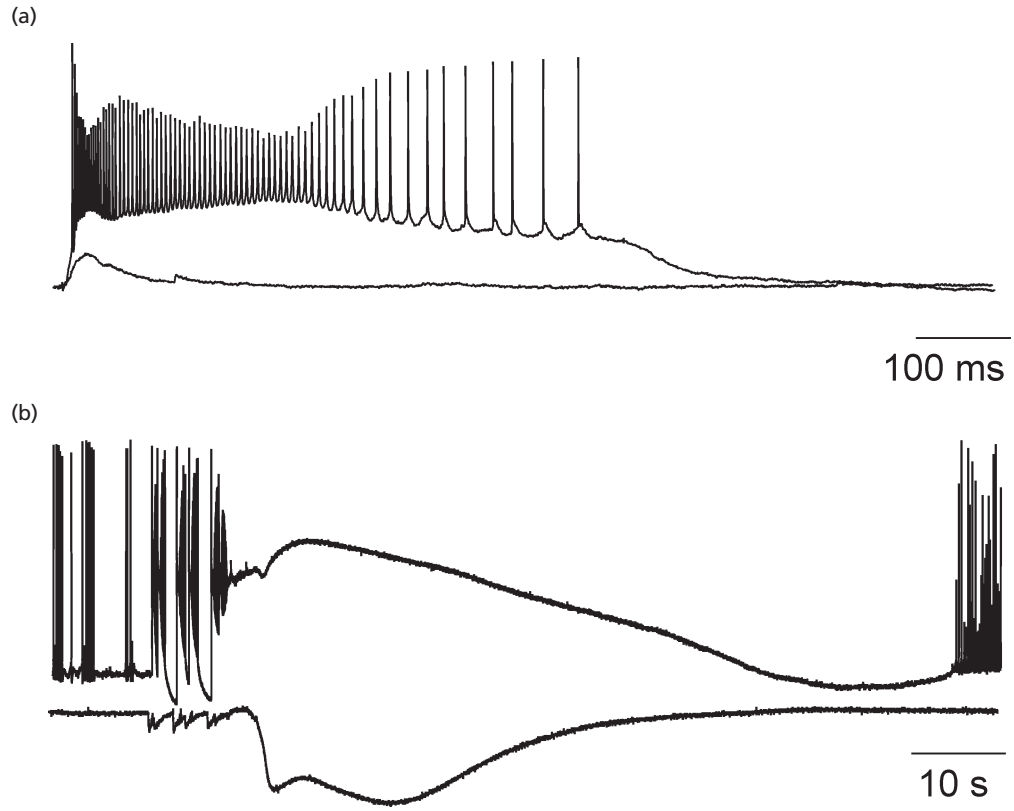

Fig. 5.1 (a) Intracellular recording from a neocortical pyramidal neurone perfused with the GABA antagonist bicuculline reveals a paroxysmal depolarization shift (PDS) evoked by an afferent synaptic stimulus. Note that a subthreshold stimulus evokes a normal excitatory synaptic potential. (b) Uppermost trace: same display as in (a) at a different time scale to show in the same cell the transition from interictal PDS to a sustained ictal discharge. Note spontaneous recurrent PDS eventually merging in a long depolarization lasting about 10 s, which is considered to represent an ictal event at cellular level. Lower trace: field recording of the discharge synchronously involving a large neuronal population.

Ion channels are hetero-oligomeric membrane proteins, typically consisting of 2–6 subunits including transmembrane segments that are assembled in a variable number of domains. This is seen in Fig. 5.2, which shows the subunit structures forming ligand- and voltage-gated channels. Fig. 5.2 also shows the disposition of N and C termini: from the extracellular side of the membrane in ligand-gated channels (receptors), and from the cytoplasmic side in voltage-gated channels. The N-terminal region is particularly important in beginning the process of subunit association that leads to channel assembly, a process that is facilitated by the presence of accessory subunits and significantly influenced by a large number of different environmental influences. It leads to the formation of channels with different degrees of permeability to the various ions and different opening and inactivating kinetics, depending on the type of subunits assembled, their stoichiometric characteristics, and the relative position of each subunit within the hetero-oligomeric complex. The contribution of channel–receptor-mediated transmembrane currents to the generation of action potential and PDS is schematically depicted in Fig. 5.3.

The identification of the molecular structure of the various subunits and their corresponding coding genes has revealed a surprising multiplicity of distinct subunits, of which the pattern of assembly can lead to a considerable number of channel subtypes with different properties [8]. When investigating the elementary determinants of neuronal excitability (e.g. ionic channels), it must be remembered that most epileptic seizures are either due to discharges generated in different parts of the neo- or paleocortices (partial seizures), or seem to arise diffusely from a large part of the cerebral cortex of both hemispheres, with the possible involvement of thalamic structures (generalized seizures). The topographic expression pattern of putative epileptogenic dysfunctions should therefore be carefully investigated, not only at structural but also at cellular and subcellular level.

Voltage-gated channels

These form a category of ion channels that undergo voltage-dependent conformational changes leading to transitions from the closed to open state or vice versa.

Na^+ channels

The molecular structure of the pore-forming α-subunit of Na^+ channels is shown in Fig. 5.2. Each domain contains six transmembrane segments, the fourth one being the voltage sensor, and the loop between the fifth and sixth forming the ion-selective pore. The cytoplasmic loop between the third and fourth domain is the inactivation point. This structure satisfactorily correlates with the functional properties demonstrated by electrophysiologi-

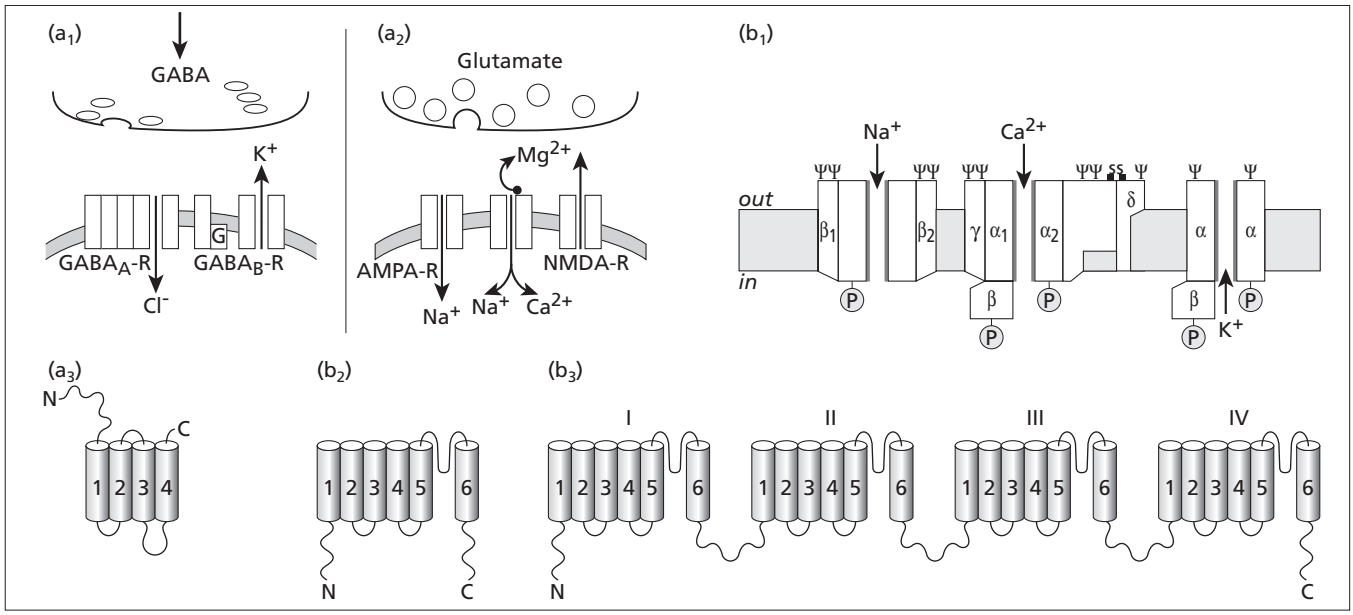

Fig. 5.2 Ligand-gated and voltage-gated channels largely involved in the paroxysmal depolarization shift (PDS) generation. The upper panels schematically represent GABAergic (a_1) and glutamatergic (a_2) synapses and Na^+, Ca^{2+} and K^+ channels (b_1). Flat and round vesicles are respectively recognizable in GABA- and glutamate-containing presynaptic endings. Ionotropic receptors (R) are depicted on the postsynaptic membrane. The lower part of the figure shows a schematic representation of the molecular structure of pore-forming subunits of ligand-gated (a_3), voltage-gated K^+ (b_2) and Na^+/Ca^{2+} (b_3) channels.

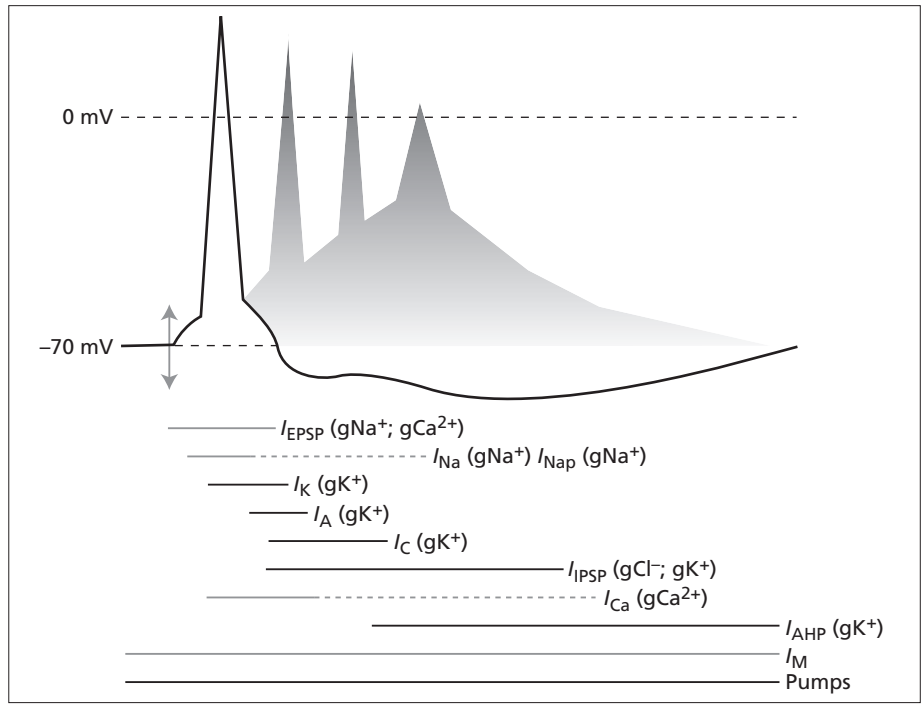

Fig. 5.3 The contribution of different transmembrane currents to the generation of action potential and paroxysmal depolarization shift (PDS). The broken line indicates the level of 0 mV membrane potential. Owing to the effect of ion pumps in resting conditions, membrane potential is kept around –70 mV. The lines below the tracings depict the time course of ion currents with different kinetics. Grey lines indicate currents that tend to depolarize the membrane and black lines indicate currents that polarize it. Particularly effective in inducing the transition from simple action potential to PDS are the currents with slow kinetics (I_{Nap}, I_{Ca}).

cal recordings, which allow characterization of the activation and inactivation kinetics of the main transient component of Na^+ current (I_{NaT}) and of the persistent Na^+ component (I_{NaP}), owing to a fraction of Na^+ channels that fail to inactivate.

Experiments with toxins that block Na^+ channel inactivation (thus considerably enhancing its persistent I_{NaP} component) have demonstrated that this effect is sufficient to switch the firing of neocortical pyramidal neurones from regular spikes to bursts [9]. The possible role of Na^+ changes in the pathophysiology of human epilepsies was first suggested on the basis of indirect arguments, such as the blocking effect of clinically effective antiepileptic drugs (AEDs) on Na^+ currents [10] and particularly I_{NaP} [11,12]

(for a review, see Stafstrom [13]). In the last 10 years, a vast amount of data revealed changes of Na^+ channel molecular structure in cases of familial generalized epilepsies with febrile seizures plus (GEFS+) (for a review, see Meisler and Kearney [14]) or simple febrile seizures [15]. The discovery of *SCN1A* mutations in patients with the non-familial severe myoclonic epilepsy of infancy (SMEI or Dravet's syndrome) [16], a drug-resistant epileptic encephalopathy [17], further indicated the importance of channel pathologies in human epilepsies and suggested that channel mutations may cause neurological disease even in the absence of a positive family history.

Heterogonous expression studies of different mutations of SCN1A channel subunits showed a large spectrum of functional effects. Many of these effects were consistent with a gain of function of Na^+ channels, and thus with a pathologically increased membrane excitability [14,18]. However, the effects of other mutations are unclear, or conversely indicate a complete loss of function. Experiments aimed at clarifying this apparently paradoxical defect suggested that the prominent presence of the mutated channel subunit on inhibitory interneurones [19,20] reduces interneurone firing, eventually resulting in the increased excitability of 'released' pyramidal neurones. This interesting topic shows the complex scenario of channel pathology and highlights the need for further investigation aimed at understanding the effect of sodium channel mutations at circuitry level rather than in individual neurones.

Another point needing clarification arises from the observation that families with identical mutations show heterogeneous phenotypes, ranging from mild expression with febrile seizures to more severe epilepsies such as myoclonic–astatic epilepsy [21]. Furthermore, even if most SMEI mutations are *de novo*, in a few cases they have been inherited from mildly affected parents [16,22]. Therefore, concomitant factors (e.g. primary non-pathogenetic factors involving other channel subunits or modulating mechanisms) are probably crucial in shaping the final effect of the mutated channels to appear as a more or less severe phenotypic expression. Recently, it has been found that molecular interactions with modulatory proteins or drugs can partially rescue the function of Na^+ channels with mutations that normally lead to a complete loss of function [23]. This evidence further shows that more research is needed to clarify the functional effects of channel mutations *in vivo* and the variability of the phenotypes resulting from Na^+ channel mutations.

K^+ channels

Unlike Na^+ and Ca^{2+} channels, which are large monomeric proteins that include four homologous repeats, K^+ channels are made by the assembly of four proteins, the basic structure of which are shown in Fig. 5.2. These assembled proteins each contain six transmembrane domains. The resulting structure is similar to that of Na^+ and Ca^{2+} channels, but the number of possible subtypes is much higher because of the large number of possible combinations. Although it is assumed that there are subtle functional differences between the different subtypes, the currents flowing to the K^+ channels are grouped in a relatively limited number of physiological categories. Other than the 'delayed rectifier', first described by Hodgkin *et al.* [24] and characterized by slow activation kinetics, the most important types of K^+ current are I_A (rapid kinetics with activation range between –65 and –40 mV); $I_{K(Ca)}$ (Ca^{2+} dependent); I_{AR} (activation in hyperpolarization); I_H (activation in hyperpolarization, carried by Na^+ and K^+); $I_{K(ATP)}$ (voltage-independent, and blocked by ATP); I_M (activation range from –60 to –20 mV, blocked by acetylcholine binding to muscarinic receptors); $I_{K(Na)}$ (activated by a high concentration of intracellular Na^+) and; I_R (inward rectifier, whose physiological significance in the central nervous system is still not completely understood).

With the exception of the I_R, all of the K^+ currents are outward currents, which means that their effect is to move the membrane potential towards the more negative value. This reduces the probability of cell discharge and/or limits the amplitude and duration of depolarizing events, whereas membrane repolarization after an excitatory event (i.e. an action potential) is the prerequisite for further action potential generation. This was first recognized by Hodgkin *et al.* [24], who used the term 'delayed rectifier' to indicate the characteristics of the repolarizing K^+ current in the giant axon of the squid. The definition was intended to denote the fact that the increase in membrane conductance (rectification) due to the opening of the corresponding K^+ channel is delayed in comparison with that of the Na^+ channel in terms of the beginning of the depolarizing pulse current used to evoke the action potential. Owing to the rich repertoire of K^+ channels with which the neurone is endowed, the K^+ currents flowing through them can modulate membrane excitability and shape excitatory events in a highly sophisticated manner.

Of particular interest here are the limiting effects of K^+ currents on the sustained depolarization underlying PDS and the high-frequency discharges of action potentials. This is probably due to the combined influence of I_K, I_A, $I_{K(Ca)}$ and $I_{K(Na)}$. However, because it is active at about the resting potential, I_M is particularly effective in distancing the threshold of the membrane potential for the generation of the high-frequency action potentials characterizing the neurones belonging to epileptic neurone aggregates. Epileptiform discharges can be easily obtained in *in vitro* preparations by perfusion with K^+ blockers such as extracellular tetraethylammonium, by intracellular Ca^{2+} or simply by increasing the K^+ concentration in extracellular fluid, which reduces the strength of the outward K^+ currents by decreasing the intracellular–extracellular K^+ concentration gradient that provides the driving force for K^+ outflow.

It has been suggested that disrupted K^+ channel function is involved in the epileptogenesis in some spontaneously occurring human epilepsies. In benign neonatal familial convulsions (BNFC), Biervert *et al.* [25] and Wang *et al.* [26] have demonstrated the pathogenetic role of a genetically determined I_M defect. Interestingly, these studies showed that two K^+ channel subunits (KCNQ2 and KCNQ3) contribute to the native M current, and that mutations of either of the genes coding for these subunits (located at the 20q13 and 8q24 chromosomal loci, respectively) lead to an impairment in the M current associated with the BNFC phenotype. The M current depends on a slowly activating and inactivating K^+ conductance; the range of this activation (–60 to –20 mV) makes the I_M particularly suitable for controlling subthreshold membrane excitability and the responsiveness to synaptic inputs.

The above studies have stimulated a new interest in K^+ currents as possible targets for new antiepileptic drugs (AEDs), as seen in a review by Rogawski [27]. The recent identification of molecules acting as KCNQ channel activators and the advances in defining the activator-binding sites have provided a new possible therapeutic strategy. Indeed, some of these drugs are capable of inducing conformational channel changes and subthreshold opening that lead to a 'gain of function' of the hyperpolarizing currents flowing through these channel types [28] and nominally to restore postexcitatory repolarization.

Ca^{2+} channels

Like Na^+ channels, the Ca^{2+} α-subunit is a large monomeric protein that includes four homologous repeats (Fig. 5.2). The characterized high-voltage activated Ca^{2+} currents are I_L (a slow current with an activation level positive to −30 mV), I_N, $I_{P/Q}$ and I_R (fast currents, activation positive to −20 mV), and it has been found that they are differently expressed in brain cells and other excitable tissue. In addition, a low-threshold I_T current that is inactive at resting membrane potential and *reactivated* by membrane hyperpolarization (activation level positive to −70 mV) has been found to be particularly pronounced in some regions of the central nervous system, such as the inferior olivary nucleus and the thalamic nuclei (see ref. 29 for a review).

As Ca^{2+} is a divalent cation, its cross-membrane movements are particularly effective in depolarizing the membrane, and so the possible role of Ca^{2+} currents in sustaining the pronounced depolarization underlying PDS has been repeatedly hypothesized. However, this is difficult to prove experimentally for three reasons: (1) given its paramount importance for protein synthesis and metabolism, a considerable amount of Ca^{2+} is stored in the cytoplasmic reticulum and any artificial change in its concentration in an experimental preparation can mobilize it from the storage compartment to the ionized free fraction, thus leading to complex effects on cell excitability that are further complicated by metabolic effects, which are often difficult to resolve; (2) the role of Ca^{2+} in promoting vesicle fusion at nerve terminals adds a presynaptic effect that has to be taken into account when evaluating membrane excitability as a function of Ca^{2+} concentration; and (3) a number of the Ca^{2+}-dependent K^+ currents contributing to cell excitability (see above) may be impaired when Ca^{2+} concentration is artificially lowered, thus leading to indirect and somehow unpredictable consequences that may obscure the direct effect of Ca^{2+} movement across the membrane.

The main evidence of the possible involvement of Ca^{2+} channels in the pathogenesis of naturally occurring epilepsies comes from experimental studies of the generalized non-convulsive epilepsies that occur in rats (the Genetic Absence Epilepsy Rat from Strasbourg, GAERS) [30], WGJ [31], mutant tottering, lethargic, stargazer and ducky mice with absence epilepsy, cerebellar degeneration and ataxia (see ref. 32 for a review).

Experiments carried out in our laboratory [33–36] indicate that overexpression of the low-threshold Ca^{2+} current in reticular thalamic nucleus (Rt) cells could be responsible for GAERS spike–wave (SW) discharges according to a mechanism which will be further specified below. Although no genetic basis for this Ca^{2+} channel dysfunction has yet been demonstrated in GAERS, mutations have been found in the genes that code for the $\alpha 1_A$-, β4-, γ2- and α2δ-subunits of the calcium channel in mutant tottering, lethargic, stargazer and ducky mice with SWs [32].

Furthermore, the role of the I_T current in the generation of SW discharges has recently been confirmed by experiments in mice lacking α1 GT-type Ca^{2+} channel [37].

Investigations aimed at confirming the role of Ca^{2+} channel mutation in the most frequent types of human non-convulsive generalized epilepsies (childhood and juvenile absence epilepsies) have been inconclusive so far; however, the evidence of a mutation of the gene *CACNA1A* coding for the P/Q Ca^{2+} channel has been recently reported in a child with early-onset absence epilepsy and cerebellar ataxia [37].

Ligand-gated channels

Ligand-gated channels, or receptors, are molecular complexes that include a pore region or ionophore, which becomes permeable to some ions when the relevant ligand binds to a specific binding site. Ligand-gated channels are classified according to a scheme based on the ligand (neurotransmitter or neuromodulator), with a number of functionally distinct subtypes being differentiated in each category based on pharmacological (affinity for artificial ligands) or physiological criteria (selective ion permeability). Increasing knowledge of the molecular structure of receptor subunits is providing grounds for defining subtypes on the basis of their structure–function relationships.

The ion currents flowing through the receptor-associated ionophores can significantly affect membrane potential and cell excitability, and so these channels too are implicated in epileptogenesis and as possible targets for AEDs. Pharmacological agents acting on receptors can affect not only the primary epileptogenic process, but also its effects in regions beyond the epileptogenic area.

Excitatory amino acid receptors

The amino acids glutamate and aspartate are the two main excitatory neurotransmitters in the cerebral cortex and act through various receptor subtypes, the subunit composition of which determines the selective ionic permeability and kinetics of the respective ionic currents [38]. From the functional point of view, two main receptor types have been identified. AMPA and NMDA are respectively named after the two ligands α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and *N*-methyl-D-aspartic acid (Fig. 5.2). The ionophores associated with both receptor types are permeable to Na^+, but the NMDA receptor is also permeable to Ca^{2+} and is blocked by Mg^{2+} in a voltage-dependent manner; consequently, the inward Na^+/Ca^{2+} current flowing through it can be activated by ligand-receptor interaction only when the membrane potential is depolarized enough to remove the Mg^{2+} block. As Ca^{2+} is a divalent cation, the NMDA-dependent I_{EPSP} is very powerful in depolarizing the membrane and can significantly enhance and prolong excitatory postsynaptic potentials (EPSPs).

The potential epileptogenic effect of EAA systems is demonstrated by the fact that a number of EAA agonists (kainic and hybotenic acids, NMDA) are currently used to induce various types of epilepsies in animals. In humans, evidence of structural changes in EAA receptors leading to AMPA or NMDA

epileptogenic hyperactivity in the dysplastic cortex has been provided by Najm *et al.* [39]. Moreover, the occurrence of circuitry rearrangements leading to a selective facilitation of the NMDA-dependent I_{EPSP} has been demonstrated in temporal lobe epilepsy and will be further discussed below.

γ-Aminobutyric acid receptors

There are two main types of GABA ionotropic receptors (A and B), which are respectively coupled to Cl^- and K^+ ionophores, as well as a metabotropic receptor that can indirectly modulate membrane excitability. Recently a third type of ionotropic receptor, $GABA_C$, has been demonstrated. The inflow of Cl^- and outflow of K^+ promoted by GABA binding to *ionotropic* receptors both lead to a membrane hyperpolarization that results in inhibitory postsynaptic potentials (IPSPs). GABA-mediated IPSPs are very effective in preventing neuronal discharges because they are associated with a dramatic drop in membrane input resistance. Local inhibitory circuits consisting of Golgi type 2 GABAergic neurones are ubiquitously present in the cerebral cortex as a mechanism controlling the main population of pyramidal neurones. $GABA_A$ blockers (bicuculline, penicillin and picrotoxin) are well-known epileptogenic agents currently being used in experimental studies. As far as human epilepsies are concerned, the evidence of a decrease in GABAergic neurones in brain tissue resected for the treatment of refractory epilepsies [40,41] has not been unequivocally confirmed by subsequent studies. The idea of the functional impairment of structurally intact GABAergic circuitry proposed by Sloviter 1991 [42] under the attractive name of the 'dormant basket cell hypothesis' was also not confirmed by recordings made of human hippocampi during presurgical evaluation for refractory temporal lobe epilepsies [43], which showed enhanced rather than impaired inhibition. Furthermore, the hyperexcitable dentate gyrus removed from patients with temporal lobe epilepsy retains bicuculline-sensitive synaptic inhibition [44]. A more recent systematic analysis of tissue specimens from cortical dysplasias revealed significant disarrangements in GABAergic circuitry [45], but their functional significance is still unclear.

One variant of the GEFS+ syndrome has been reported to be associated with a mutation of the *GABRG2* gene that codes for the γ2-subunit of the $GABA_A$ receptor [46,47], and a defect in the *GABRB3* gene that codes for the β3-$GABA_A$ receptor subunit is thought to account for the epileptic symptoms of Angelman's syndrome [48]. GABA receptor genes and their relation to idiopathic generalized epilepsies have been repeatedly investigated but the results derived from the study of individual large families or few smaller families have been still contradictory (see ref. 49 for a review). On the other hand, the GABA function plays a varying role in different brain structures or in different developmental epochs. It is certainly well known that impairment of cortical GABAergic transmission obtained by the application of GABA receptor antagonists or by targeted genetic mutations induces epileptic seizures. However, various drugs increasing GABAergic transmission are currently used for antiepileptic therapy in humans. The antiepileptic and proepileptogenic effects of GABAergic drugs in subcortical structures, namely in the thalamus, are still not clearly understood. Various studies indicated a proepileptogenic role of $GABA_B$ in absence seizures, probably depending on the complex interaction between pre- and postsynaptic receptors [50].

A special form of GABA-dependent excitation occurs in early developmental stages, when GABA release, occurring before synapse formation, plays as a neurotrophic factor rather than a neurotransmitter and regulates neuronal migration [51]. In early life, GABA neurotransmission matures sooner than glutamate neurotransmission and has a plastic effect. However, owing to the presence of an immature distribution of Cl^- across the membrane, the immature GABA depolarizes the neuronal membrane, thus acting as an excitatory neurotransmitter (see ref. 52 for a review). A similar paradoxical GABA-dependent depolarization, resulting in an excitatory action, can reappear in the adult brain in specific epileptogenic conditions [53].

Acetylcholine receptors

Acetylcholine (ACh) receptors are present ubiquitously in the central nervous system, but their role in controlling brain excitability is much less known than that of the receptors in the peripheral nervous system, where ACh is the main excitatory neurotransmitter at neuromuscular junctions. As it could be obtained in very large quantities from the electric organ of the *Torpedo marina*, the ACh receptor was the first to be purified and characterized [54]. Its pore region has a pentameric structure consisting of various hetero- or homologous combinations of eight α-subunits and three β-subunits.

Phillips *et al.* [55] identified a large Australian family including 27 subjects affected by autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) with a linkage for locus 20q13.2 in 1995 and, subsequently, Steinlein *et al.* [56] discovered the mutation of the *CHRNA4* gene that codes for the α4-subunit of the nicotinic ACh receptor, and thus provided the first demonstration of a human epilepsy due to a genetically determined channel alteration. It has been shown that mutations of the *CHRNB2* gene coding for the β2-subunit of ACh receptors lead to similar phenotypes. The effect of these mutations on ACh receptor gating remains to be determined, as does their role in neuronal hyperexcitability. As the α4-subunit is widely distributed in the mammalian brain, it is puzzling how the mutation can cause a focal hyperexcitability syndrome.

Circuit involvement in epileptogenesis

Although an alteration in neuronal excitability is a primary prerequisite for epileptogenesis, epileptic discharges cannot be due to the abnormal activity of individual neurones, but require the synchronous activation of large populations of hyperexcitable neurones. The generation and spread of epileptic discharges therefore needs to be considered.

Local circuits

The special role of the physiologically bursting IB neocortical and hippocampal neurones mentioned in the introduction depends not only on the power of their excitatory output, but also on their pattern of connectivity, which makes them particularly suitable for the synchronization of large populations of synaptically connected neurones.

Layer V intrinsically bursting pyramidal neurones of the neocortex

Chagnac-Amitai and Connors [57] have shown that one-third of the layer V pyramidal neurones of the rat neocortex are endowed with intrinsically determined bursting properties and generate axon collaterals running tangentially to the cortical surface, which establish synaptic connections with a large number of neighbouring pyramidal neurones. They also demonstrated that pyramidal IB neurones consistently fire in association with highly synchronized electrocorticographic potentials, thus confirming their presumed synchronizing ability. It is interesting to note that the bursting discharges of neocortical IB neurones are determined by the persistent fraction of the Na^+ current I_{NaP} [58,59] and so it can be expected that inherited or acquired changes in Na^+ channels (the putative epileptogenic role of which has been discussed above) may also enhance the IB-dependent synchronizing mechanism, especially if they affect Na^+ channel inactivation.

Taken together, the available data suggest that the synchronizing circuitry established by layer V IB pyramidal neurones of the neocortex plays an important role in recruiting the 'critical mass' of neurones required to create an epileptogenic area.

Intrinsically bursting neurones of CA3

All cornu ammonis area 3 (CA3) neurones have an intrinsically determined bursting property, which, unlike that of neocortical IB neurones, is Ca^{2+} dependent [60]. However, in functional terms, CA3 and neocortical IB neurones are similar in so far as their connectivity enables them to synchronize the activity of synaptically connected neuronal populations. The anatomical basis is the Shaeffer's collateral of the CA3 neuronal axons, which establish a rich synaptic connectivity with the dendrites of the pyramidal neurones of cornu ammonis area 1 (CA1). The effectiveness of this synaptic organization can be easily demonstrated in *in vitro* hippocampal slices by placing a stimulation electrode on the CA3 stratum radiatum, after which the synchronized CA1 output is conveyed to the hippocampal–entorhinal circuitry that creates the reverberating loop involving dentate gyrus–CA3/CA1–entorinal cortex–dentate gyrus. Dreier and Heinemann [61] have developed a technique for preparing *in vitro* slices including the full circuit, and demonstrated that it is necessary and sufficient to sustain persistent epileptic activities (Fig. 5.4). The physiology of this multisynaptic system and its relevance to epilepsy have been a focus of intense research.

In addition to the Na^+ and K^+ conductance responsible for action potentials, both the granule cells making up the principal population of the fascia dentata and the pyramidal cells of Ammon's horn also possess a broad repertoire of Ca^{2+} and K^+ conductance (including Ca^{2+}-dependent K^+ conductance) that contribute towards modulating their firing properties. In particular, the Ca^{2+} conductance is responsible for generating the depolarizing afterpotential (DAP) that follows the action potential, whereas the Ca^{2+}-dependent K^+ conductance is essentially responsible for the pronounced afterhyperpolarizing potential (AHP) that follows individual or repetitive (burst) action potentials. The CA3 pyramidal cells have a marked DAP, which keeps the membrane depolarized and determines burst discharges with a much greater degree of probability than that observed in CA1. In contrast, the granule cells have much shorter DAPs and, under physiological conditions, rarely produce burst discharges. They are therefore particularly suited to the production of graduated activities that are linearly correlated with the intensity of the stimulus, whereas the CA3 cells can act as amplifiers capable of having a secondary effect on the CA1 cells through Schaeffer's collateral projection that make up the exit stage of the circuit. Both the fascia dentata and Ammon's horn contain GABAergic interneurones that are activated directly by the fibres in arrival (feed forward inhibition) as well as by the axonal collaterals of the principal cells (feedback inhibition). An important property of the hippocampal–entorhinal circuit is plasticity and it will be discussed in the next section.

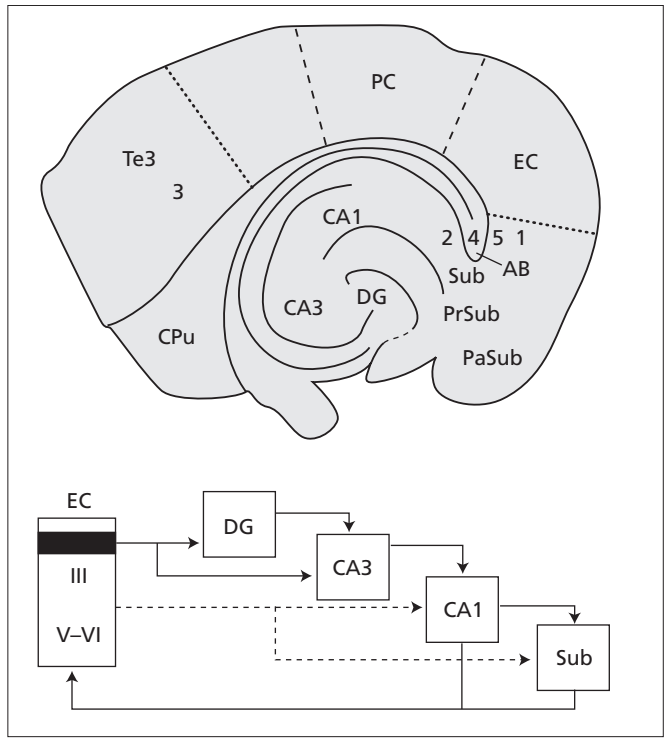

Fig. 5.4 Uppermost part: brain slice of the hippocampal formation prepared according to the Dreier and Heinemann technique. Te3, neocortical temporal area 3; PC, parahippocampal cortex; EC, entorhinal cortex; hippocampal formation with the dentate gyrus is shown in areas CA3 and CA1; Sub, PrSub, PaSub, subiculum, pre- and para-subiculum; CPu, caudat putament. In the lowermost part of the figure, the reciprocal connections of the above structures creating the hippocampal–entorhinal circuitry are represented by a wiring diagram. From ref. 61, with permission.

There is no evidence of primary functional or anatomical CA3 neuronal alterations in human epilepsies but CA3 and its efferent connections can be secondarily involved as a consequence of other circuit changes occurring in human mesial temporal lobe epilepsy (MTLE), as is discussed in the next section.

Systems

Thalamocortical system

It has long been known that thalamocorticothalamic circuits play a role in the generation of SW discharges [62,63]. The results

obtained in rodents presenting with absences associated with 7-Hz SW [64,65] have shed some light on the SW-released rhythmogenic properties with which thalamocortical circuitry is endowed [34–36,66].

A key role is played by the reticular thalamic (Rt) nucleus, a laminar structure enfolding the anteroventral and lateral aspects of the dorsal thalamus that is entirely made up of GABAergic neurones. Rat neurones have a low-threshold Ca^{2+} current (I_T) that is particularly effective in generating sequences of 7–9 Hz Ca^2/K^+-dependent bursts after hyperpolarizing complexes [33,67]. The resulting rhythmic GABAergic output is fed into the thalamocortical relay (TCR) neurones, which are therefore recruited in rhythmic firing with a reciprocal time relationship. A simplified sequence of the events occurring during an SW discharge is schematically illustrated in Fig. 5.5. Both the thalamic nuclei and the cortex are necessary to sustain the SW-related oscillatory mode of thalamocortical circuitry as selective lesions or functional block of either thalamic nuclei [34] or cortex can suppress SW discharges. Moreover mice lacking α(1G) T-type Ca^{2+} channels show a lack of the burst firing of thalamocortical relay neurones and resistance to absence seizures [37]. Whether SW-related thalamocortical activity is initiated in the thalamus [36] or in the cortex [68] has long been debated. Recent results [69,70] support a crucial role of facial somatosensory cortex as a trigger area of SW-related oscillatory activity in thalamocortical systems of rodents. Recent evidence indicates that a non-inactivating Na^+ current component may act synergistically with the T-type Ca^{2+} current [71].

Limbic system

The series of structures located at the edge of the cerebral mantle and surrounding the hilum of the hemisphere was first called the limbic lobe (grand lobe limbique) by Broca in 1878 [72]. The limbic system is involved with the integration of emotions and autonomic functions. The main limbic structure and its interconnections are schematically depicted in Fig. 5.6. Among the subcallosal, cingulate and parahippocampal circumvolutions, the hippocampus and dentate gyrus and the amygdala are involved in generation and propagation of those epileptic seizures that are characterized by autonomic symptoms and often referred to as limbic seizures.

Hippocampus and parahippocampal cortex

The hippocampus is the main part of the archicortical component of the oligostratified cortex or archicortex. Some information concerning the significance of integrative hippocampal activities has come from studies of the correlations between cell activities and behaviour. Above all, these have demonstrated a fundamental relationship between the discharging properties of hippocampal

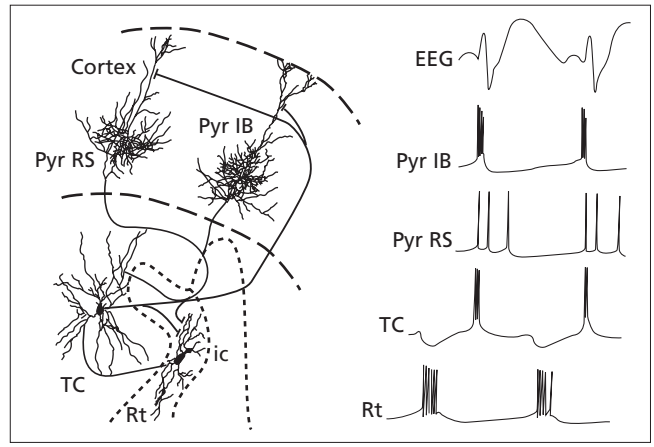

Fig. 5.5 The reverberating thalamocorticothalamic circuit putatively responsible for spike–wave (SW) discharges. Low-threshold Ca^{2+} current in reticular neurones (Rt) gives rise to particularly pronounced burst-hyperpolarization sequences which induce rhythmic inhibitory post-synaptic potentials (IPSPs) in thalamocortical (TC) neurones. The resulting membrane hyperpolarization allows activation of a low-threshold Ca^{2+} current in TC neurones that sustain rebound burst in reciprocal time relationship with Rt. The TC excitatory output propagates to the cortex where both regular spiking and intrinsically bursting pyramidal neurones (PyrRS, PyrIB) are excited simultaneously and send their rhythmic output back to thalamic Rt and TC neurones. The synchronous discharges of cortical neurones are 'seen' by the electroencephalograph scalp electrodes as rhythmic spike–wave complexes. SW discharges are thought to result from a pathological enhancement of the oscillations in the circuitry. From ref. 35.

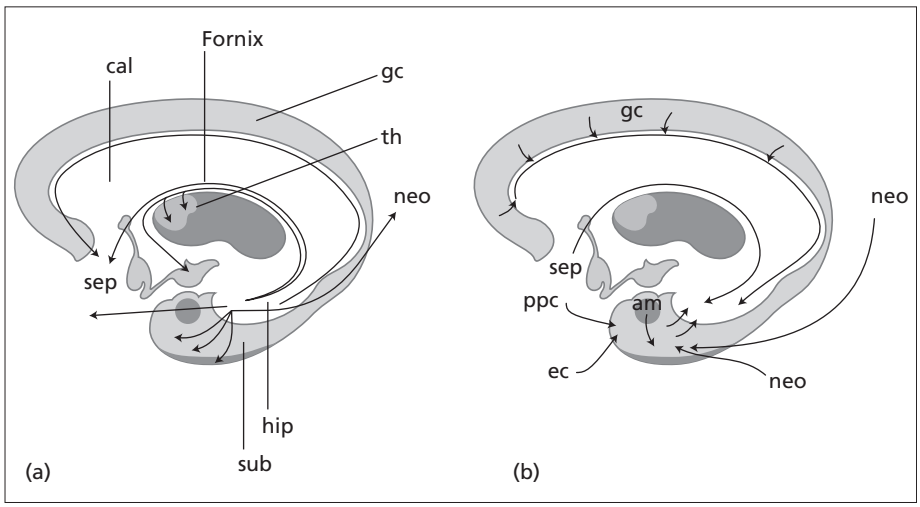

Fig. 5.6 Limbic circuitry. The arrows in parts (a) and (b) indicate efferent and afferent connections, respectively. am, amygdala; cal, corpus callosum; ec, entorhinal cortex; gc, gyrus cinguli; hip, hippocampus; neo, neocortex; ppc, prepyriform cortex; sep, septum; sub, subiculum; th, anterior thalamic nuclei.

cells and arousal, the most important finding being the modifications created during the acquisition of conditioned responses. These modifications are the expression of a synaptic plasticity that was experimentally characterized by Bliss and Lømo [73], who demonstrated that high-frequency stimuli of the entorhinal cortex could persistently increase the effectiveness of synaptic transmission to granule cells and termed this effect *long-term potentiation* (LTP). Thanks to these properties, the limbic (and particularly hippocampal) circuits are capable of recording and storing traces of information originating from the various sensory systems by constructing a cognitive map that is continuously updated on the basis of experience [74]. The relevance of hippocampal plasticity in the pathophysiology of temporal lobe epilepsies was first demonstrated by Graham Goddard [75]. Goddard coined the term *kindling* to describe the phenomenon whereby the repeated subthreshold stimulation of susceptible structures induces an epileptiform EEG and increasingly prolonged and severe behavioural abnormalities. Eventually spontaneous seizures occur. The role of such an epileptogenic plasticity in determining the progressive course of some types of epilepsies will be discussed further in the next section.

Amygdala

The amygdaloid complex includes various nuclei that are involved in integrative activities connected with the association of emotional and neutral stimuli, with the control of homeostasis and with the utilization of current and memorized experiences [76]. Sensory information reaches the amygdala through the lateral nucleus and is then distributed in parallel to the various other nuclei by means of a system of highly organized intra-amygdaloid circuits. Amygdala discharges are often associated with oral feeding automatisms (chewing movements) that are sometimes accompanied by salivation [77], less frequently with unmotivated fear and even more rarely with emotional expressions of anger and aggressiveness described in classic animal studies [78].

Cingulate gyrus

The cingulate region appears to be involved in conditioned responses presumably connected with the acquisition of avoidance reactions. The symptomatology of epileptic seizures originating from the anterior cingular region includes terror, screams, aggressive verbal expressions, complex gestural automatisms, vegetative disturbances and visual hallucinations associated with only partial alterations in consciousness [79]. The anatomical basis underlying the motor expression of the responses are the connections between this region and the caudate nucleus, the ventral pontine nuclei, the ventral part of the periaqueductal grey matter, and the deep strata of the superior colliculus. The posterior or retrosplenial cingulate region seems to be particularly involved in the processes of spatial discrimination associated with visual information.

Other fibre systems

Corticocortical connections can provide epileptic discharges with a number of propagation pathways that may account for the large variety of epileptic phenomena. Specific mention should be made of the role of frontal callosal projections in the interhemispheric synchronization of epileptic discharges. Marcus and Watson [80] reported that bilateral frontal homotopic epileptogenic foci in rhesus monkeys produced bilateral discharges resembling bilateral synchronous SW, but symmetrical foci located in other parts of the cortex were usually independent. They obtained different types of pseudogeneralized discharges depending on the location of the bilateral frontal loci, a finding that correlates well with the marked tendency towards the bilateral expression of seizures with a frontal origin in humans.

Epileptogenesis as a process

In several instances epilepsy, i.e. a chronic condition of the brain characterized by an enduring propensity to generate epileptic seizures, seems to be the result of a process that develops progressively from an initial event. The biological mechanisms responsible for this progressive course of the epileptogenic process have been extensively investigated as potential targets of strategies to prevent the development of epilepsy. One important question is whether the seizures themselves can activate mechanisms capable of facilitating epileptogenesis. The obvious difficulty is with the differentiation of cause and effect, i.e. to determine whether epilepsy becomes progressively worse owing to high seizure frequency or whether high seizure frequency is the expression of an epileptogenic process which is, per se, severe from the beginning.

There is evidence that the progressive course of epileptogenic changes in excitable mechanisms (i.e. ion channels and receptors) and circuitry may account for a progression of epilepsy towards a more severe condition with a reduced sensitivity to AED treatment.

Channels and receptors

Changes in Na^+ channel subunit expression have been reported in the hippocampal tissue from experimental animals [81,82] and from patients with temporal lobe epilepsy [83]. These molecular changes result in the enhancement of Na^+ current, which can contribute to epileptogenesis [82]. Relevant to epileptogenesis are the changes in expression of glutamate and GABA receptor subunits reported in human tissue from experimental animals [84,85] and patients with temporal lobe epilepsy [86,87]. Moreover, complex changes in neurotransmitter and neuromodulator systems have been reported (see ref. 88 for review), which can participate in epileptogenic mechanisms. Particular attention has been devoted to the neuromodulatory action of neuropeptides, namely neuropeptide Y, which is overexpressed in the hippocampus of various seizure models. Neuropeptide Y inhibits glutamatergic transmission and has been proposed to act as an endogenous anticonvulsant [89] and could therefore be a privileged target for gene therapy [90].

Circuitry

An impressive number of data demonstrate that in several instances epileptogenesis is associated with circuitry reorganization. The first evidence was provided by Sutula *et al.* [91], who first demonstrated that the kindling process is associated with the sprouting of a mossy fibre pathway that reorganizes synaptic connections in the dentate gyrus, and then that a similar picture can be observed in the surgically resected hippocampus of patients with epilepsy [92]. These findings have been confirmed by others [93]. Mossy fibre sprouting had been previously observed after

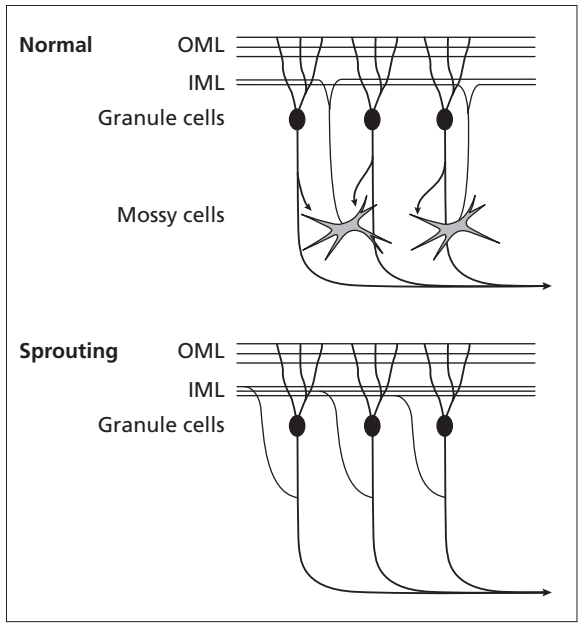

Fig. 5.7 Schematic representation of granule axon sprouting in hippocampal sclerosis. According to the current interpretation, the inner molecular layer, deprived of the mossy fibres because of the degeneration of hilar mossy cells, is reoccupied by newly formed axon collaterals of granule cells. IML, inner molecular layer; OML, outer molecular layer.

experimentally induced status epilepticus accompanied by extensive neural damage (e.g. in the kainic acid model [94]), but the kindling paradigm demonstrated that repeated brief seizures can induce sprouting in the absence of initial extensive brain damage [95]. In human MTLE, mossy fibre sprouting is consistently associated with hippocampal sclerosis and cell loss, and it is thought that the degeneration of mossy cells of the hippocampal hilus significantly contributes to the circuitry rearrangement (Fig. 5.7).

Experiments in various animal models have shown that sprouted mossy fibres make synaptic contacts in ectopic locations, and thus provide an excitatory feedback circuit [96–98]. The excitatory effect of the aberrant recurrent fibres is further enhanced by the facilitation of NMDA receptor-mediated conductance, which has been demonstrated in dentate granule cells in slices prepared from the surgically excised temporal lobe tissue of epileptic patients [99]. Recurrent axon collaterals also make synaptic contacts with inhibitory interneurones, leading to an enhanced inhibition [100] that, rather than preventing the generation of epileptic discharges, contributes to it by promoting synchrony [101]. The main dentate granule axon target is CA3 (which is therefore secondarily involved in the hyperexcitable state) but it is not known to what extent the sprouted collaterals of granule axons inside CA3 contribute to the enhanced excitability in postsynaptic neurones, nor the contribution of sprouting phenomena occurring elsewhere in the hippocampal-entorhinal circuit, such as in CA1 [102].

In general, it can be said that the study of circuit reorganization in MTLE has provided important insights into its biological bases but left a number of unanswered questions. Comparisons of human and animal studies have shown that brief seizure episodes can set in motion a cascade of events leading to sprouting and neosynaptogenesis, which may account for the tendency of MTLE to progress towards a condition of medical intractability.

In both humans and experimental animals (kainic and pilocarpine models), there is a typical biphasic time course, with a more or less prolonged latent interval between the initial event and the chronic epileptic phase, during which the activation of Ca^{2+}-dependent proteases, protein kinase C, Ca^{2+}/calmodulin kinase systems and the immediate early gene [103] promotes circuit remodelling. The most frequent initial event in the clinical history of MTLE is a prolonged febrile seizure during the first 2 years of life that can be likened to the status epilepticus induced by kainic acid and pilocarpine in experimental animals. Once established, the aberrant hippocampal circuitry creates a condition of hyperexcitability that leads to chronic epilepsy, which is often difficult to treat.

However, a number of other observations do not support this linear interpretation. First of all, experimental interventions that prevent sprouting do not impair the acquisition of epileptic properties [104]. Second, although PDS-like discharges can easily be recorded from dentate granule cells in *in vitro* sclerotic hippocampal slices and putatively interpreted as the result of newly formed glutamatergic synapses, *in vivo* recordings taken from the epileptogenic hippocampi of patients indicate that bursting neurones are only rarely encountered and that it is difficult to demonstrate their synchrony [105,106]. Third, the role of the putatively seizure-dependent cell loss in determining the sprouting is still unclear, as is that of the excess of zinc caused by the sprouting of zinc-containing mossy fibres upon glutamatergic and GABAergic synaptic transmission [107]. Finally, the relevance of seizure-stimulated modulations of adult neurogenesis in the dentate gyrus to human MTLE [108] remains to be clarified.

Whichever is its role in MTLE pathogenesis, sprouting remains an important morphological correlate of epileptogenesis and a better knowledge of its neurobiological mechanisms can advance our understanding of epileptogenesis. Much effort is being devoted to identify investigational tools by which the development of epileptogenesis could be monitored. Staba *et al.* [109] have recently shown a correlation between histopathological changes found in hippocampal sclerosis and high-frequency oscillations (fast ripples) recorded with depth electrodes from patients with medically intractable MTLE. Should it be possible to record such activities with non-invasive methods, fast ripples could provide an interesting marker of the epileptogenic process.

In recent years the role of inflammation in epileptogenesis has been intensively investigated [110,111], prompting Annamaia Vezzani and her group [112] to propose a novel anticonvulsant strategy based on the inactivation of the interleukin-converting enzyme caspase-1.

Another modern approach is aimed at identifying genes that may affect the development of an epileptogenic process set in motion by a non-genetic mechanism. A recent review of Lukasiuk *et al.* [113] reveals that epileptogenic insults induce time-specific expression of genes relevant to different aspects of epileptogenesis, such as cell death and survival, neural plasticity and immune responses, suggesting novel lines of research that may advance our understanding of epileptogenesis.

Conclusions

Many different types of experimental manipulations affecting neuronal excitable properties can induce epileptic discharges in various *in vivo* and *in vitro* models of epilepsy. Over the last few years, a number of cell mechanisms involving voltage-dependent and ligand-operated channels have been found to be relevant to human epilepsies. An important step was the identification of some monogenic epilepsies due to mutations of genes coding for ion channels or receptors (epileptogenic channelopathies). This has led to a greater understanding of how these elementary alterations can affect brain circuitry in some common types of human epilepsies. The term 'system epilepsies' has recently been proposed to describe this [114]. The data relating to seizure-related brain plasticity are particularly interesting because they shed further light on the biological bases for epileptogenesis and for the tendency of some epilepsies to progress towards a condition of medical intractability. New data on brain inflammation in epilepsy and epileptogenesis indicate that a better understanding of the genetic basis of these phenomena will likely open the way to further exciting progress in the not too distant future.

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6 Antiepileptic Drug Discovery

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Epilepsy affects more than 50 million people worldwide and consists of more than 40 clinical syndromes [1]. At the present time, treatment strategies are symptomatic, rather than curative, in nature and aimed at the suppression of clinical seizures with one or more of the available antiepileptic drugs (AEDs). Since the early 1990s, 10 new AEDs have been approved for the add-on treatment of partial seizures. Moreover, there are several more AEDs in late-stage clinical development. This has been an exciting era for the physician treating patients suffering from seizure disorders, and for the patient with epilepsy the introduction of the new drugs continues to provide renewed hope for complete seizure control and lessening of their AED-associated side-effect profile. Never before has there been so many new AEDs available for the management of epilepsy.

As with any other class of drugs, the discovery and development of new AEDs rely heavily on the preclinical employment of animal models to establish efficacy and safety prior to their introduction in human volunteers. Obviously, the more predictive the animal model for any given seizure type or syndrome, the greater is the likelihood that an investigational AED will demonstrate efficacy in human clinical trials. Unlike many other central nervous system (CNS) disorders, epilepsy has benefited from reasonably predictive animal models, particularly models that predict efficacy against primary generalized and partial seizures. Nonetheless, one of the most often discussed issues has focused on what model(s) is most appropriate when attempting to screen for efficacy against human epilepsy.

This chapter will review the different approaches employed in the AED discovery process and how each of these has led to the successful identification of clinically effective AEDs. In addition, it will address some of the issues surrounding the development of more appropriate models of pharmacoresistant seizures. An extensive discussion of these issues is beyond the scope of this chapter. Where possible, the reader will be referred to pertinent reviews for a more detailed discussion.

Characteristics of the ideal model system

In a perfect world, the 'ideal' screening model should reflect similar pathophysiology and phenomenology to human epilepsy. In addition, seizures should evolve spontaneously in a developmental time frame consistent with the human condition and display a pharmacological profile that is resistant to existing AEDs. Given the limitless potential of combinatorial chemistry to identify potential therapies, it would be preferable if a given animal model were amenable to high-volume screening. Unfortunately, human epilepsy is a heterogeneous neurological disorder that encompasses many seizure phenotypes and syndromes. As such, it is highly unlikely that any one animal model will ever predict the full therapeutic potential of an investigational AED. This necessitates the evaluation of an investigational AED in several syndrome-specific model systems.

The current era of antiepileptic drug discovery

Since 1974, the National Institutes of Neurological Disorders and Stroke (NINDS) has played a pivotal role in stimulating the discovery and development of new chemical entities for the symptomatic treatment of human epilepsy, through its Anticonvulsant Screening Project, which, since its inception, has accessioned over 30 000 investigational AEDs from academic and pharmaceutical chemists worldwide. The majority of these investigational AEDs have evolved from one of the following strategies: random drug screening and efficacy-based AED discovery; structural modification of a clinically effective pharmacophore; and mechanistic-based AED development. The University of Utah Anticonvulsant Drug Development Program uses a battery of well-defined animal models to provide initial characterization of the anticonvulsant and behavioural toxicity profile [2–5]. The remainder of this chapter will review the current systematic screening process employed by the Anticonvulsant Drug Development Program at the University of Utah and discuss some of its inherent advantages and limitations. Subsequent discussion will focus on some of the emerging models that may be more likely to identify the truly 'novel' AED for the treatment of pharmacoresistant partial epilepsy.

The current era of AED discovery was ushered in by Putnam and Merritt [6] in 1937, when they demonstrated the feasibility of using the maximal electroshock seizure (MES) model to identify the anticonvulsant potential of phenytoin. Since then, different animal models have been used. A number of new AEDs have been developed since 1993 and are currently in development (second-generation AEDs). Although they have improved therapy, these drugs have not altered the percentage of patients with 'therapy-resistant' partial epilepsy; e.g. there has been no

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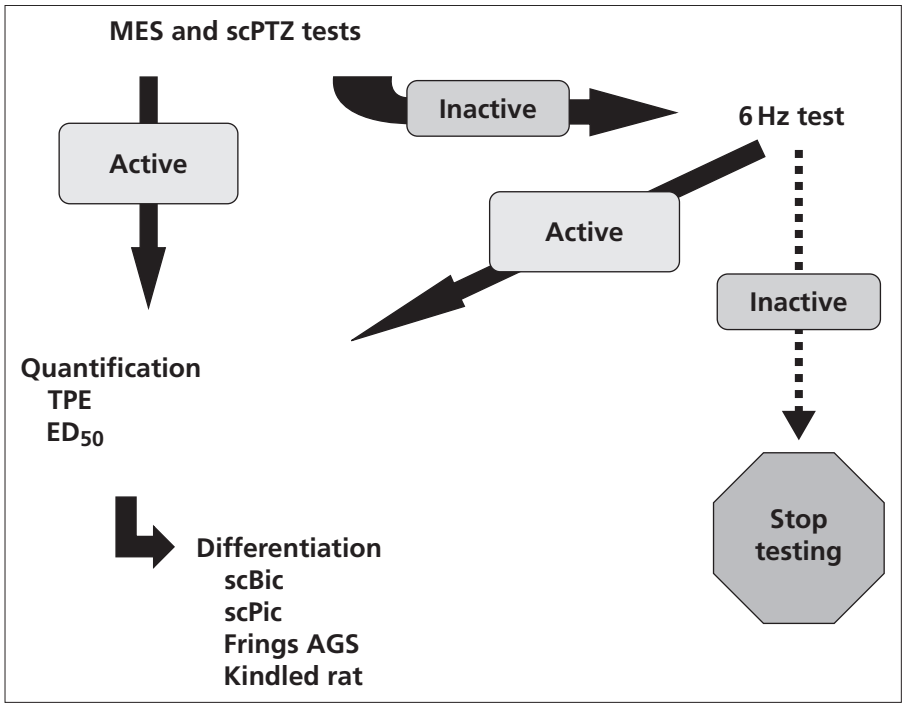

Fig. 6.1 The initial identification screen of the University of Utah Anticonvulsant Screening Project. Once accessioned, an investigational AED is screened for efficacy in both the MES and scPTZ tests. The activity of those compounds (median effective dose, ED_{50}) with demonstrated efficacy and minimal behavioural toxicity is quantitated at the time to peak (TPE) anticonvulsant effect. Compounds found inactive in the MES and scPTZ tests are subsequently evaluated in the 6-Hz seizure test. The activity of those compounds with demonstrated efficacy in the 6-Hz test is then quantitated at their respective time to peak effect. All compounds found active in one or more of these three identification screens are then differentiated on the basis of their activity in the subcutaneous bicuculline (scBic) test, the subcutaneous picrotoxin (scPic) test, the Frings audiogenic seizure-susceptible (AGS) mouse, and the hippocampal kindled rat model of partial epilepsy.

significant change since the early 1970s and the percentage remains between 25% and 40% [7].

Identification of anticonvulsant activity

As shown in Fig. 6.1, the University of Utah Anticonvulsant Screening Project undertakes three primary screens in their initial identification studies. These are the MES, subcutaneous pentylenetetrazol (scPTZ), and 6-Hz psychomotor seizure tests. Each of these evoked seizure models provides valuable information regarding the potential anticonvulsant spectrum of an investigational AED.

Maximal electroshock seizure and subcutaneous pentylenetetrazol tests

The MES and scPTZ seizure models continue to represent the two most widely used animal seizure models employed in the search for new AEDs [5,8,9] and currently remain as the primary screens of the Anticonvulsant Screening Project (Fig. 6.1). As mentioned above, Putnam and Merritt [6] successfully used the MES test in a systematic screening programme to identify phenytoin. This observation, when coupled with the subsequent success of phenytoin in the clinical management of generalized tonic–clonic seizures, provided the validation necessary to consider the MES test as a reasonable model of human generalized tonic–clonic seizures. In 1944, Everett and Richards [10] demonstrated that PTZ-induced seizures could be blocked by trimethadione and phenobarbital but not by phenytoin. A year later, Lennox demonstrated that trimethadione was effective in decreasing or preventing petit mal attacks in 50 patients but was ineffective or worsened grand mal attacks in 10 patients [11]. Trimethadione's success provided the necessary validation to establish the PTZ test as a model of petit mal or generalized absence seizures. With these observations, the current era of AED screening using the MES and scPTZ tests was launched.

The MES and scPTZ tests are routinely conducted with either mice or rats. For the MES test, individual animals receive an electrical stimulus that is delivered through either corneal or pineal electrodes for a 0.2 s duration. The stimulus is of sufficient intensity (e.g. 50 mA in mice and 150 mA in rats) to induce a tonic extension seizure characterized by hindlimb extension. This stimulus intensity is typically three to five times greater than the threshold current necessary to evoke a maximal seizure. An investigational drug is said to offer protection in the MES test if it displays an ability to block the hindlimb tonic extensor component of the seizure.

In the scPTZ test, PTZ is administered subcutaneously in a dose sufficient to produce a minimal clonic seizure of the vibrissae and/or forelimbs that persists for at least 5 s. A drug is said to be effective in the scPTZ test if it is able to block the minimal clonic seizure described above. It is important to note that higher doses of PTZ can produce myoclonic jerks, repeated clonic seizures of the vibrissae, forelimbs and hindlimbs without loss of righting reflex, clonic seizures of the limbs with loss of righting reflex and loss of righting reflex followed by tonic extension of the forelimbs and hindlimbs [12]. These different endpoints are associated with different pharmacological profiles [12,13]. For example, ethosuximide and phenytoin (two AEDs with markedly different clinical profiles) will both block threshold tonic extension seizures induced by scPTZ [13].

The anticonvulsant activity of those AEDs found to be active at non-toxic doses in the initial identification studies is then quantitated in a larger population of mice or rats. For these studies, the MES and scPTZ tests are routinely conducted at the predetermined time to peak effect of the investigational

Table 6.1 Correlation between anticonvulsant efficacy and clinical utility of the established and second-generation AEDs in experimental animal models.[a]

Experimental model	Clinical seizure type			
	Tonic and/or clonic generalized seizures	Myoclonic/generalized absence seizures	Generalized absence seizures	Partial seizures
MES (tonic extension)[b]	Carbamazepine, phenytoin, valproate, phenobarbital (felbamate, gabapentin, lamotrigine, pregabalin, topiramate, zonisamide)			
scPTZ (clonic seizures)[b]		Ethosuximide, valproate, phenobarbital[c], BZD (felbamate, gabapentin, tiagabine[c], pregabalin, vigabatrin[c])		
Spike–wave discharges (absence seizures)[d]			Ethosuximide, valproate, BZD (lamotrigine, topiramate, LVT)	
Electrical kindling (focal seizures)				Carbamazepine, phenytoin, valproate, phenobarbital, BZD (felbamate, gabapentin, lamotrigine, pregabalin, topiramate, tiagabine, zonisamide, LVT, vigabatrin)
6 Hz (44 mA)[e]				Valproate (LVT)

[a] BZD, benzodiazepines; CBZ, carbamazepine; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LTG, lamotrigine; LVT, levetiracetam; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.
[b] Data summarized from ref. 5.
[c] PB, TGB and VGB block clonic seizures induced by scPTZ but are inactive against generalized absence seizures and may exacerbate spike–wave seizures.
[d] Data summarized from refs 22,37–39.
[e] Data summarized from ref. 16.

drug following oral or intraperitoneal administration to either mice or rats. Numerous technical, biological and pharmacokinetic factors have been identified which can 'qualitatively' affect the results obtained in a drug test [12,14,15]. These factors, albeit important, are not likely to overlook an active drug in the MES and scPTZ tests but can contribute to false conclusions regarding the potency and duration of action of an active drug.

The MES and scPTZ tests are easily conducted with a minimal investment in equipment and technical expertise. They provide valuable data regarding the potential anticonvulsant activity of an investigational drug, and with one exception, levetiracetam, all of the currently available AEDs and AEDs in clinical development have been found to be active in one or both of these tests (Table 6.1). Furthermore, both tests are amenable to high-volume screening with widely available, relatively inexpensive, normal rodents. As the MES and scPTZ tests are conducted in 'pathologically normal' rodents, there is no guarantee that they will be equally effective in 'pathologically abnormal' rodents. The best example to illustrate this point is levetiracetam. As mentioned above, the MES and scPTZ tests failed to identify levetiracetam's anticonvulsant activity. Subsequent investigations demonstrated that levetiracetam was active in 'pathologically abnormal' models of partial and primary generalized seizures [16–20]. In this regard, levetiracetam has, since its discovery, been considered to represent the first 'truly' novel AED identified in recent years and has underlined the need for flexibility when screening for efficacy and the need to incorporate levetiracetam-sensitive models into the early evaluation process.

As shown in Table 6.1, neither of these seizure models possesses a pharmacological profile consistent with therapy-resistant human epilepsy. The MES test is sensitive to all of the first-generation AEDs effective in the treatment of generalized tonic–clonic seizures (e.g. phenytoin, carbamazepine, valproate and phenobarbital) and a number of the second-generation AEDs (e.g. felbamate, gabapentin, pregabalin, lamotrigine, lacosamide, topiramate and zonisamide). Likewise, the scPTZ test is sensitive to those first-line AEDs used in the management of generalized absence seizures (i.e. ethosuximide, valproate and the benzodiazepines) and some second-generation compounds (felbamate, gabapentin, pregabalin, tiagabine and vigabatrin). However, these two models were initially validated using the older, established AEDs phenytoin, phenobarbital and trimethadione [4,8] and it could be argued that the continued use of these methods leads to the identification of only drugs with a similar pharmacological profile (see refs 4 and 8 for historical review and discussion). However, when initially used, there was a limited armamentarium of AEDs available and several of the drugs possessed significant teratogenic properties or safety issues (e.g. trimethadione, bromide and phenobarbital) and there was a clear need for improved products.

One might ask then what, if any, benefit these two tests might provide when screening for novel AEDs. First, both tests provide some insight into the central nervous system bioavailability of a particular investigational AED. Furthermore, both models are

non-selective with respect to mechanism of action. As such, they are very well suited for the early evaluation of anticonvulsant activity because neither model assumes that a particular drug's pharmacodynamic activity is dependent on its molecular mechanism of action. For example, the MES test predicts efficacy for a broad range of mechanistically distinct AEDs including Na^+ and K^+ channel blockers, NMDA (*N*-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonists, and α2δ ligands. Similarly, the scPTZ test has been found to identify T-type Ca^{2+} channel blockers, benzodiazepines, barbiturates, GABA transport blockers, GABA transaminase inhibitors and α2δ ligands.

Lastly, both model systems display clear and definable seizure endpoints and require minimal technical expertise. This, coupled with lack of dependence on molecular mechanism, makes them ideally suited to screen large numbers of chemically diverse entities. Levetiracetam taught the community that lack of efficacy in either of these tests does not translate into lack of human efficacy. As such, there is no longer any reason to limit further screening on the basis of results obtained in the MES and scPTZ. In fact, there is no a priori reason to assume that a novel AED will be active in the MES, scPTZ or other acute seizure tests.

The 6-Hz seizure test

As discussed above, levetiracetam is unique among the clinically available AEDs in that it is inactive in both the MES and scPTZ tests, emphasizing the need to identify and characterize new screening models so as to minimize the risk of missing other potentially novel AEDs. To this end, the Anticonvulsant Drug Development Program is currently utilizing the 6-Hz psychomotor seizure model in its early identification studies (Fig. 6.1) [5,21].

Although the high-frequency (50 Hz), short-duration (0.2 s) stimulation used in the MES test has become a standard for screening AEDs, it was only one of several electroshock paradigms initially developed in the 1940s and 1950s [22]. An alternative stimulation paradigm was the low-frequency (6 Hz) long-duration (3 s) corneal stimulation model that was stated to produce 'psychic' or 'psychomotor' seizures. Instead of the tonic extension seizure characteristic of the MES test, the 6-Hz seizure test was reported to involve a minimal clonic phase followed by stereotyped, automatistic behaviours reminiscent of human partial seizures [23–25]. At the time of its initial description, the authors were attempting to validate the 6-Hz model as a screening test for partial seizures; however, the pharmacological profile was not consistent with the profile observed in clinical practice [25]. For example, phenytoin was found to be inactive in the 6-Hz seizure test. This observation led to the view that it was no more predictive of clinical utility than the other models available at the time (i.e. the MES and scPTZ tests). Subsequent investigations in our laboratory confirmed the relative insensitivity of the 6-Hz test to phenytoin and also to carbamazepine, lamotrigine and topiramate [21]. The relative resistance of some patients to phenytoin and other AEDs in today's clinical setting and the lack of sensitivity of the MES and scPTZ to levetiracetam prompted studies to re-evaluate the 6-Hz seizure test as a potential screen for therapy-resistant epilepsy [21]. Subsequent investigations demonstrated that levetiracetam did afford protection against the 6-Hz seizure at a stimulus intensity at which other AEDs display little to no efficacy (Table 6.2). Of the drugs in late-stage clinical development, efficacy in the 6-Hz test has also been confirmed for brivaracetam, carisbamate, lacosamide and retigabine. This observation clearly demonstrates the potential utility of this model as a screen for novel AEDs that may be useful for the treatment of therapy-resistant partial seizures.

Table 6.2 Effect of stimulus intensity on the anticonvulsant efficacy (ED_{50}, mg/kg i.p.) of phenytoin, lamotrigine, ethosuximide, levetiracetam and valproic acid in the 6-Hz seizure test.

Antiepileptic drug	Stimulus intensity (mA)		
	22	32	44
Phenytoin	9.4 (4.7–14.9)	>60	>60
Lamotrigine	4.4 (2.2–6.6)	>60	>60
Ethosuximide	86.9 (37.8–156)	167 (114–223)	>600
Levetiracetam	4.6 (1.1–8.7)	19.4 (9.9–36.0)	1089 (787–2650)
Valproic acid	41.5 (16.1–68.8)	126 (94.5–152)	310 (258–335)

Results are represented as ED_{50} (95% confidence interval). With permission from ref. 21.

Differentiation of anticonvulsant activity

Once the efficacy of an investigational AED is established using either the MES, scPTZ or 6-Hz seizure test, a battery of further tests are employed to characterize the anticonvulsant potential of the test substance. These include assessing the ability of the investigational AED to block audiogenic seizures in the Frings audiogenic seizure-susceptible mouse, limbic seizures in the hippocampal kindled rat and acute clonic seizures induced by the γ-aminobutyric acid A ($GABA_A$) receptor antagonist bicuculline or the Cl^- channel blocker picrotoxin [3,5,8].

Of these tests, the kindled rat is the only chronic model currently employed by the Anticonvulsant Drug Development Program. Kindling is defined as the progressive increase in electrographic and behavioural seizure activity in response to repeated stimulation of a limbic brain region such as the amygdala or hippocampus with an initially subconvulsive current [26]. The kindled rat is a useful chronic model for identifying those AEDs that are likely to be useful for the treatment of difficult-to-control seizure types such as complex partial seizures [27]. To this point, the Anticonvulsant Screening Project has initiated studies to evaluate the efficacy of investigational AEDs in the lamotrigine (LTG)-resistant kindled rat. In addition to its utility in AED discovery, the kindled rat also provides a means of studying complex brain networks that may contribute to seizure spread and generalization from a focus [28]. The kindling process is associated with a progressive increase in seizure severity and duration, a decrease in the focal seizure threshold and neuronal degeneration in limbic brain regions that resemble human mesotemporal lobe epilepsy. The electrographic and behavioural components of the kindled seizure begin locally at the site of stimulation and quickly become secondarily generalized. In 1972, Racine [29] proposed a behavioural scoring system that is still in use today. The Racine scale provides a quantitative efficient mechanism through which to assess the effect of an investigational AED on the focal (stages

1 and 2) or secondarily generalized (stages 3–5) seizure. In addition to the behavioural seizure, one can assess whether the drug of interest also affects the electrographic seizure.

One of the kindling models employed by the Anticonvulsant Drug Development Program is the rapid hippocampal kindling model of Lothman *et al.* [28]. This particular model offers some distinct advantages for the screening and evaluation of new anticonvulsant substances, and provides a framework for assessing, in a temporal fashion, drug efficacy in a focal seizure model. For most drug studies, the candidate substance is evaluated for its ability to block the evoked kindled motor seizure (seizure scores of 3–5) and limbic behavioural seizure (seizure score between 1 and 2) and to affect changes in the afterdischarge duration. The kindled rat is also an important tool that can be used to identify drugs that prevent or attenuate the development of a seizure focus (i.e. antiepileptogenic versus anticonvulsant drugs). Thus, in an acquisition paradigm, animals begin receiving the test substance prior to initiation of the kindling process. The relevance of a drug's ability to delay or prevent the development of kindling to human epileptogenesis remains unknown. Valproic acid, phenobarbital, levetiracetam, topiramate and several NMDA antagonists are among some of the drugs found to delay the acquisition of kindling. Of these, valproic acid has been examined for its ability to prevent the development of post-traumatic epilepsy following closed head injury [30,31]. In this study, valproic acid was quite effective in preventing the acute seizures but it failed to prevent the development of epilepsy. Although not conclusive, this finding would suggest that the kindling model is perhaps not a predictive model of trauma-induced epilepsy. Whether it is more predictive of other acquired epilepsies is not known at the present time. As mentioned above, the AED discovery programme at the University of Utah has utilized the LTG-resistant kindled rat in recent years to differentiate the pharmacological profile of novel AEDs. The LTG-resistant kindled rat model of partial epilepsy was first described by Postma and colleagues (2000) [32]. In this particular model, resistance to LTG is induced when a rat is exposed to low-dose LTG during the kindling acquisition phase. For example, exposure to a low dose (5 mg/kg) of LTG during kindling development leads to reduced efficacy of LTG when administered to the fully kindled rat [32]. A similar phenomenon has been observed for carbamazepine [33]. Perhaps more important is the observation that LTG-resistant rats are also refractory to carbamazepine, phenytoin, and topiramate but not valproate or the investigational $KCNQ_2$ activator retigabine [34–36] or the investigational AED carisbamate [37].

The LTG-resistant kindled rat offers the practical advantage over the phenytoin (PHT)-resistant rat [38,39] that it is not necessary to prescreen a population of rats in order to identify those animals that are pharmacoresistant. It serves as an early model to differentiate novel AEDs from phenytoin, lamotrigine, carbamazepine and topiramate.

Pharmacological profile and potential clinical utility

Although not predictive of therapy-resistant epilepsy, the pharmacological profile of the MES, scPTZ and kindled rat tests does provide some insight into the potential clinical utility of drugs that are found to be active in one or both of these tests. For example, the pharmacological profile of the MES test clearly supports its utility as a predictive model for human generalized tonic–clonic seizures and, to date, all of the clinically evaluated drugs that have demonstrated efficacy in the MES test have been found to possess activity against generalized tonic–clonic seizures. In contrast, the lack of any demonstrable efficacy by tiagabine, vigabatrin and levetiracetam in the MES test argues against its utility as a predictive model of partial seizures. Consistent with this conclusion is the observation that NMDA antagonists are very effective against tonic extension seizures induced by MES; however, they were found to be without benefit in patients with partial seizures [40].

Historically, positive results obtained in the scPTZ seizure test were considered suggestive of potential clinical utility against generalized absence seizures. This interpretation was based largely on the finding that drugs active in the clinic against partial seizures (e.g. ethosuximide, trimethadione, valproic acid, the benzodiazepines) were able to block clonic seizures induced by scPTZ,whereas drugs such as phenytoin and carbamazepine, which were ineffective against absence seizures, were also inactive in the scPTZ test. Based on this argument, phenobarbital, gabapentin and tiagabine should all be effective against spike–wave seizures but lamotrigine should be inactive against spike–wave seizures. However, clinical experience has demonstrated that this is not the case, and, for example, the barbiturates, gabapentin and tiagabine all aggravate spike–wave seizure discharge, and lamotrigine has been found to be effective against absence seizures. Thus, before any conclusion concerning potential clinical utility against spike–wave seizures is made, positive results in the scPTZ test should be corroborated by positive findings in other models of absence, such as the γ-butyrolactone [41] seizure test, the genetic absence epileptic rat of Strasbourg [42] or the lethargic (*lh/lh*) mouse [43,44]. The pharmacological profile of these three models more reasonably predicts efficacy against spike–wave seizures than the scPTZ test (Table 6.1). Another important advantage of all three of these models is that they accurately predict the potentiation of spike–wave seizures by drugs that elevate GABA concentrations (e.g. vigabatrin and tiagabine), drugs that directly activate the $GABA_B$ receptor and the barbiturates.

The 6-Hz seizure test appears to offer some of the same advantages afforded by the MES, scPTZ and kindled rat models. For example, the 6-Hz seizure test, like the MES test, is an acute electrically evoked seizure using standard corneal electroshock. It requires minimal technical expertise and is high throughput. The 6-Hz test differs from the MES tests in two respects, i.e. the frequency (6 Hz vs. 50 Hz) and duration (3 s vs. 0.2 s) of the stimulation used. The seizure that is evoked by this low-frequency, long-duration stimulus is thought to more closely model human limbic seizures and is characterized by immobility, forelimb clonus, Straub tail and facial automatisms [21,25]. In particular, the pharmacological profile of the 6-Hz test clearly differentiates itself from the other models and is dependent on the intensity of the stimulation used. For example, as the stimulus intensity is increased from the CC_{97} (convulsive current required to evoke a seizure in 97% of the mice tested) to twice the CC_{97}, the

pharmacological profile shifted from being relatively non-discriminating to being very discriminating (Table 6.2). For example, at the CC_{97} (22 mA) all of the AEDs tested (phenytoin, lamotrigine, ethosuximide, levetiracetam and valproic acid) were active at doses devoid of behavioural toxicity. In contrast, at a current intensity twice the CC_{97} (44 mA), the 6-Hz seizure was resistant to ethosuximide, phenytoin and lamotrigine but sensitive to levetiracetam and valproic acid, albeit the potency of both drugs at two times the CC_{97} was markedly reduced [21]. The observation that levetiracetam was active at a specific stimulus intensity at which other anticonvulsants display little to no efficacy illustrates the value of the 6-Hz model, as levetiracetam is inactive in the acute seizure models such as the MES and PTZ seizure tests [45,46]. The 6-Hz test may thus represent a potential therapy-resistant model and is a rather inexpensive alternative to the extremely labour-intensive and expensive chronic models such as kindling. The incorporation of this simple acute screen also minimizes the chances of 'missing' a unique drug like levetiracetam, an important consideration when setting up an anticonvulsant testing protocol to evaluate investigational AEDs.

Of the four models discussed in some detail, the kindled rat model offers perhaps the best predictive value. For example, it is the only model that adequately predicted the clinical utility of the first- and second-generation AEDs including tiagabine and vigabatrin. Furthermore, the kindled rat is the only model that accurately predicted the lack of clinical efficacy of NMDA antagonists [47]. The reason for not using the model as a primary screen is logistical. It is extremely labour intensive and requires adequate facilities and resources to surgically implant the stimulating/recording electrode, to kindle and to house sufficient rats over a chronic period of time, and is inherently time-consuming. This severely limits the number of AEDs that can be screened in a timely manner.

Recommendations

Activity of a test substance in one or more of the electrical and chemical tests described above will provide some insight into the overall anticonvulsant potential of the compound. However, a concern voiced in recent years is that the continued use of the MES and scPTZ tests in the early evaluation of an investigational AED is likely to identify 'me too' drugs and is unlikely to discover those drugs with different mechanisms of action. It has been argued that the inclusion of a kindling model into the initial identification screen would provide a mechanism to identify those novel compounds that are active in a chronic model that might be missed by the acute models currently used in the initial identification screens. In this regard, it will be of further interest to assess whether the 6-Hz screen identifies molecules that will be inherently active in the kindled rat model.

A review of the data summarized in Table 6.1 clearly demonstrates the importance of employing multiple models in any screening protocol when attempting to identify and characterize the overall potential of a candidate AED substance, as shown by the example of levetiracetam, tiagabine and vigabatrin [48,49]. Furthermore, as mentioned above, the exacerbation of spike–wave seizures by vigabatrin or tiagabine would have been predicted not by the scPTZ test but by the other models (i.e. GAERS and the *lh/lh* mouse) [44]. What is clear is the need to evaluate each investigational AED in a variety of seizure and epilepsy models. Only then will it be possible to gain a full appreciation of the overall spectrum of activity for a given investigational drug.

What is the future of AED discovery and development?

Since its inception in 1975, the NIH-based Anticonvulsant Screening Project at the University of Utah has screened over 30 000 investigational AEDs in one or more of the animal models discussed above. Of these, the Anticonvulsant Screening Project played a pivotal role in the initial identification of anticonvulsant activity for felbamate, lacosamide and topiramate, and confirmed and expanded the anticonvulsant profile for many of the other AEDs, including gabapentin, lamotrigine and levetiracetam. In addition to the compounds that have been successfully developed, another 16 compounds are in various stages of clinical development. Each of these drugs has brought about substantial benefit to the patient population in the form of increased seizure control, increased tolerability and better safety and pharmacokinetic profiles. Unfortunately for 25–40% of epilepsy patients, there still remains a need to identify therapies that will more effectively treat their therapy-resistant seizures, and there is thus a continued need to identify and incorporate more appropriate models of refractory epilepsy into the AED screening process.

Pharmacoresistant seizure models

The identification and characterization of one or more model systems that would predict efficacy in the pharmacoresistant patient population would be a valuable asset to the epilepsy community. In addition to being useful for therapy development, the ability to segregate animals on the basis of their responsiveness or lack of sensitivity to a given AED would (i) be useful for attempting to understand the molecular mechanisms underlying pharmacoresistance; (ii) be an asset for those studies designed to assess whether it is possible to reverse drug resistance; and (iii) be useful for identification of surrogate markers that might predict which patient will remit and become pharmacoresistant. At the present time, there are no clinically validated models of pharmacoresistant epilepsy. Furthermore, until that first drug or therapy is developed that has a marked effect on this patient population, we will not know what is the 'best' model system to employ in our search for more effective therapies. At the present time, the drug discovery programme at the University of Utah uses two *in vivo* models and one *in vitro* model in its attempt to characterize the full potential of a novel therapy. These include the 6-Hz limbic seizure test, the lamotrigine-resistant kindled rat model (discussed above) and the *in vitro* hippocampal slice model (see ref. 50 for a review and discussion). All three of these models meet the pivotal criteria for 'pharmacoresistance' as defined by the participants of two National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS)/

American Epilepsy Society (AES)-sponsored Workshops on Animal Models held in 2001 and 2002 [51,52], e.g. all three models 'demonstrate resistance' to two or more of the first-line AEDs employed in the treatment of partial epilepsy.

In addition to the 6-Hz psychomotor seizure model of partial epilepsy [21] and the LTG-resistant kindled rat [32,34–36] a number of additional *in vivo* model systems have been described in recent years which display a phenotype consistent with pharmacoresistant epilepsy (see ref. 53 for review). These include the PHT-resistant kindled rat [38,39], post-status epilepticus models of temporal lobe epilepsy [54–62], and the methylazoxymethanol (MAM) acetate *in utero* model of nodular heterotopia [63]. In addition to the *in vitro* entorhinal cortex–hippocampal slice model [50] and the *in vitro* low-magnesium hippocampal slice preparation [64] several other *in vitro* systems have been described over the years which meet the criteria of pharmacoresistance (see refs 65 and 66 for review and references).

Of the many models currently employed in the discovery and differentiation of investigational AEDs, the post-status epilepticus model of refractory epilepsy is beginning to emerge as an important tool. The post-status model fulfils one very important characteristic of the ideal model system: spontaneous recurrent seizures (SRS) following a species-appropriate latent period [51,52]. This model can be used to evaluate the efficacy of a given treatment on seizure type (i.e. focal or generalized), frequency of seizures, and the liability for tolerance development following chronic treatment. It also provides a mechanism to differentiate a given compound from the established AEDs. Unfortunately, these models are laborious, time-consuming and require a greater level of technical expertise. To date, they have been used in only a few pharmacological studies [54–62].

Lastly, it is important to note that the use of the post-status epilepticus rat and other models of pharmacoresistance has led to the development of novel drug testing protocols in animals that more closely resemble human clinical protocols. Furthermore, these models provide a unique biological platform for gaining greater insight into the mechanisms underlying pharmacoresistant epilepsy, to test novel approaches designed to overcome or reverse therapy resistance and to identify appropriate surrogate markers of pharmacoresistance.

Disease modification

At the present time, there are no known therapies capable of modifying the course of acquired epilepsy. Attempts to prevent the development of epilepsy following febrile seizures, traumatic brain injury and craniotomy with the older established drugs have been disappointing (see refs 30 and 31 for review). Any successful human therapy will necessarily be identified and characterized in a model system that closely approximates human epileptogenesis, and at the present time there are several potential chronic animal models in which spontaneous seizures develop secondary to a particular insult or genetic manipulation (for review and references, see refs 7 and 67). If we are to be successful in identifying a novel, disease-modifying therapy in the near future, we will need to characterize and incorporate such models of epileptogenesis into screening protocols.

Summary

This chapter has focused on the present-day process used by the University of Utah Anticonvulsant Screening Project to evaluate the anticonvulsant efficacy of an investigational AED. An attempt has been made to identify and discuss the advantages and limitations of this approach and the various animal model systems employed. Lastly, the rationale and need to broaden the scope of AED screening protocols to include models of therapy resistance and epileptogenesis has also been discussed in context with the continuing need to identify more efficacious drugs for the 25–40% of patients who remain refractory to the currently available AEDs. The real future of epilepsy research lies in our ability to couple a greater understanding of the pathophysiology of epilepsy at the molecular level with the identification and development of a truly novel therapy that modifies the course of epilepsy or prevents the development of epilepsy in the susceptible individual.

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7 Mechanisms of Antiepileptic Drug Action

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Despite a burgeoning in epilepsy research, we are still a long way from understanding the mechanisms underlying seizure generation and epileptogenesis. Antiepileptic drugs have been developed either through serendipity, such as the fortuitous discovery of the antiepileptic effects of bromides and phenobarbital, or through screening in animal epilepsy models. Indeed, the recent growth in antiepileptic drug development has been due to extensive screening of over 25 000 compounds in animal epilepsy models. Designing antiepileptic drugs with specific mechanisms of action is a recent approach that has not been particularly fruitful, first, because the drugs turn out to have separate mechanisms of actions (e.g. lamotrigine and gabapentin) and, second, because most of these drugs have been ineffective or have had unacceptable side-effects [e.g. *N*-methyl-D-aspartate (NMDA) antagonists]. Because of this, the mode of action of antiepileptic drugs is multifarious, and often poorly defined. Most antiepileptic drugs have a number of putative targets, and it is often not possible to discern which are the most germane. There may be many complex effects, even when an antiepileptic drug ostensibly has one target [e.g. tiagabine inhibiting γ-aminobutyric acid (GABA) uptake]. Rather than describe the possible mechanisms underlying each antiepileptic drug in turn (this is covered in individual chapters), we have described the more important targets of antiepileptic drugs, and which drugs affect those targets. Those that are most relevant to our present armamentarium of antiepileptic drugs are sodium channels, calcium channels and the GABAergic system. Other putative and potential targets include hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, potassium channels, the glutamatergic system, synaptic vesicle protein SV2A and some amines.

Main targets

Sodium channels

Sodium channels provide the major target for a number of antiepileptic drugs (Table 7.1). Passage of ions through voltage-gated sodium channels is responsible for the rising phase of the action potential in excitable cells and membranes, and the channels are therefore critical for action potential generation and propagation [1]. The sodium channel exists in three principal conformational states: (1) at hyperpolarized potentials the channel is in the resting closed state; (2) with depolarization the channel converts to an open state that conducts sodium ions; and (3) the channel then enters a closed, non-conducting, inactivated state. This inactivation is removed by hyperpolarization (Fig. 7.1). In this manner, depolarization results in a transient inward sodium current that rapidly inactivates. There is also a slow inactivated state which occurs with sustained depolarizations, and from which the channel recovers at hyperpolarized potentials over a matter of seconds [1].

The sodium channel consists of a 260-kDa α-subunit that forms the sodium-selective pore (Fig. 7.2). This α-subunit consists of four homologous domains (I–IV) that each consist of six α-helical transmembrane segments (S1–S6). The S4 segments are responsible for the voltage-dependent activation, as these are highly charged. Inactivation is mediated by a 'hinged lid', consisting of the intracellular loop connecting domains III and IV that can close only following voltage-dependent activation [1].

In the central nervous system, the α-subunit is associated with two auxiliary β-subunits (β_1 and β_2) that influence the kinetics and voltage dependence of the gating. There are at least 10 different sodium channel isoforms ($Na_v1.1$–1.9 and Na_x). Five of these isoforms are present in the central nervous system – $Na_v1.1$–1.3, $Na_v1.5$ (in the limbic system) and $Na_v1.6$. These isoforms have some functional differences that are of physiological importance (see below). In addition, the sodium channel can be modulated by protein phosphorylation, which affects the peak sodium current, and the speed and voltage dependence of channel inactivation [1].

Many drugs, including certain anaesthetics and antiarrhythmics, exert their therapeutic effect by preferential binding to the inactivated state of the sodium channel [1]. This has two effects: first to shift the voltage dependence of inactivation towards the resting potential (i.e. the channels become inactive at less negative membrane potentials) and, second, to delay the return of the channel to the resting, closed conformation following hyperpolarization. Phenytoin, lamotrigine and carbamazepine have a similar mode of action [2]. All bind in the inner pore of the sodium channel, and their binding is mutually exclusive, suggesting binding to identical or common amino acids [2]. There may, however, be differences in the fashion in which drugs interact with adjacent amino acids that can partly explain drug-specific effects [3]. In addition, the kinetics of antiepileptic drug interactions with the sodium channel differ, so that, for example, carbamazepine binds less potently, but faster, than phenytoin [4]. How does this binding mediate their anticonvulsant effect? The conventional

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Table 7.1 Drugs that act on voltage-gated sodium channels.

Main action
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Importance unknown
Lacosamide
Rufinamide
Topiramate
Valproate
Zonisamide
Only at high concentrations
Phenobarbitone
Benzodiazepines

view has been that such binding prevents sustained repetitive firing [5]. The rate at which an axon can 'fire' is critically determined by the rate at which the sodium channels change from the inactivated state to the resting, closed state ready to be opened by a subsequent depolarization. If this time is delayed, then the 'refractory period' is prolonged. Thus, phenytoin, carbamazepine and lamotrigine all prolong the 'refractory period' and so inhibit sustained repetitive firing. In addition, since these drugs bind to channels in their inactive state, the greater the number of channels that have entered this state, the greater the drug binding. This results in a 'use-dependent' phenomenon in which repetitive firing results in greater amounts of the drug bound and so greater inhibition. Since these drugs have a slow rate of binding to the sodium channel, there is little binding of the drug to sodium channels following a single rapid action potential, and more substantial binding only with sustained depolarizations or repetitive firing.

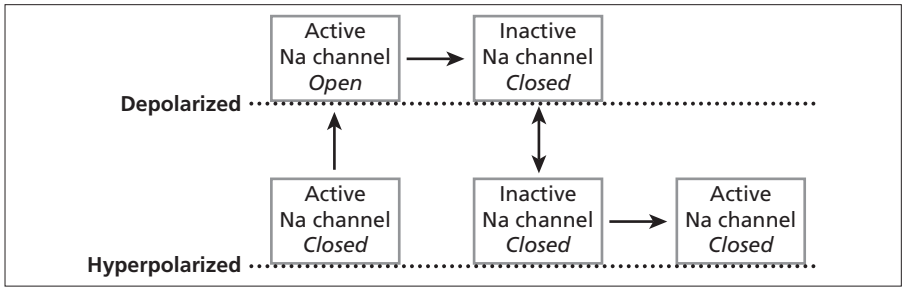

Fig. 7.1 Voltage dependence of sodium channel. In the activated state, the channel is opened by depolarization. The channel then inactivates, and hyperpolarization is necessary for reactivation of the channel.

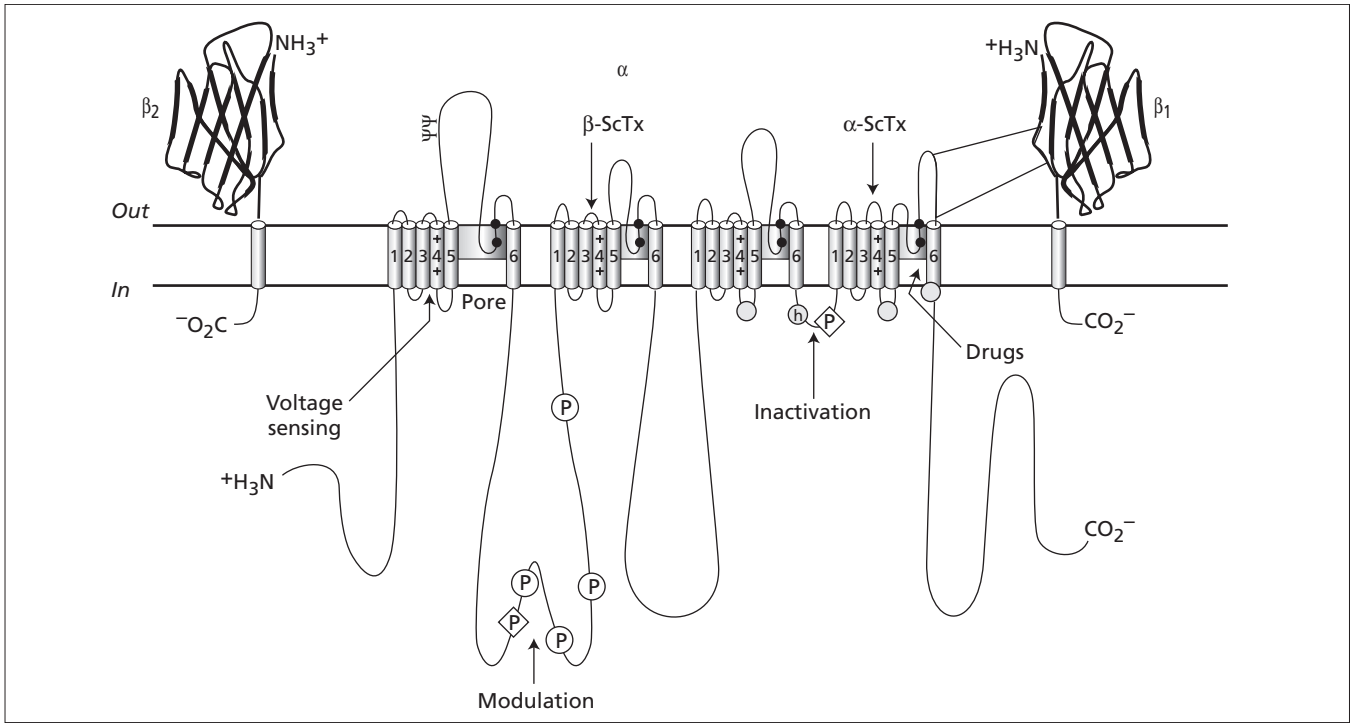

Fig. 7.2 The primary structure of the voltage-gated sodium channel consisting of four homologous six α-helical transmembrane segments (S1–6). P, sites of demonstrated protein phosphorylation by protein kinase A (PKA) (circles) and protein kinase C (PKC) (diamonds); between 5 and 6, pore-lining segments; +4+, S4 voltage sensors; h, inactivation particle in the inactivation gate loop; stippled circles, sites implicated in forming the inactivation gate receptor. Putative site of drug action is shown. From ref. 1.

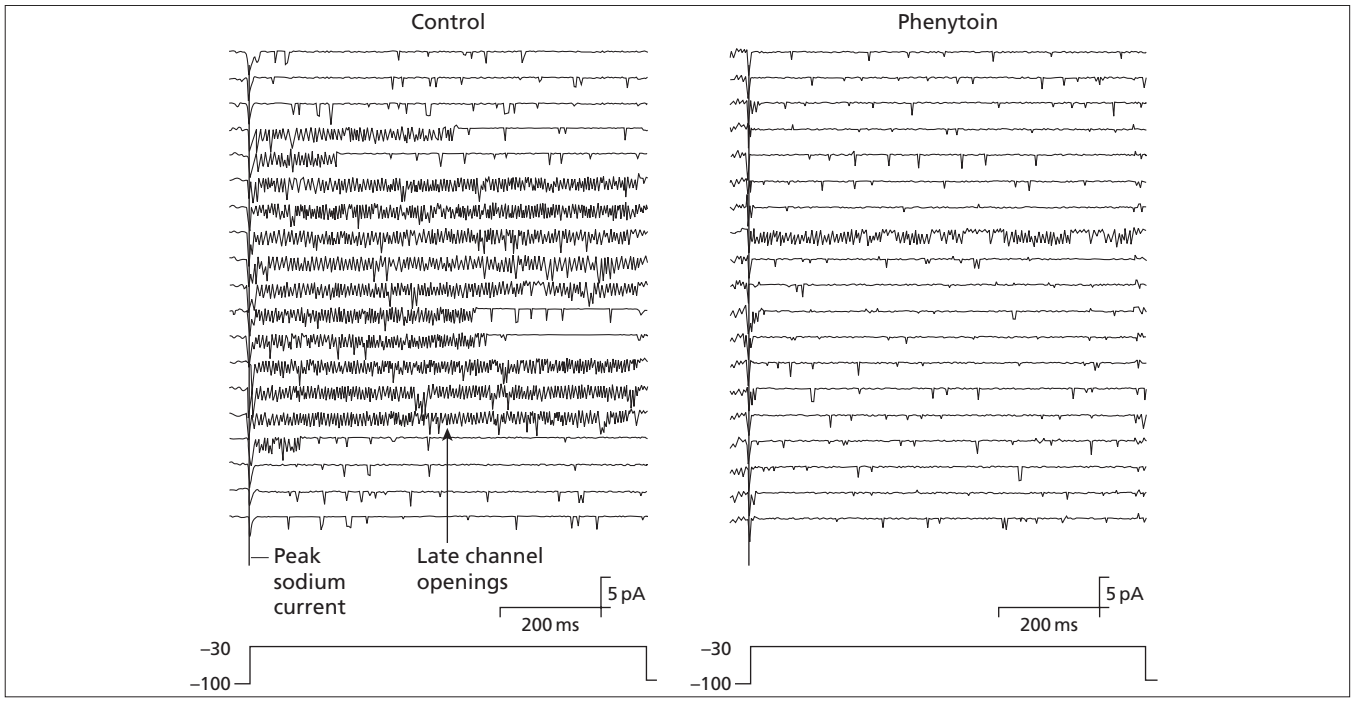

Fig. 7.3 Using outside-out patches from neuronal cultures; each record shows a consecutive trace. Sodium channels open with depolarization (peak current), followed by late channel openings. Phenytoin reduces the initial peak current, but more impressively reduces the late channel openings. From ref. 6.

Although an action on sustained repetitive firing may be one potential antiepileptic action, an action on persistent sodium currents is possibly of greater importance [6].

The persistent sodium current consists of rare late openings of sodium channels following a depolarization. Certain channel subtypes, such as $Na_v1.6$, are more prone to these late openings. Epileptiform activity is reflected, at a cellular level, by persistent depolarizations (paroxysmal depolarizing shifts), and persistent sodium currents can be a significant component of these persistent depolarizations. Prolonged late openings would permit significant drug binding, and, thus, phenytoin, carbamazepine and lamotrigine should affect the persistent current to a much greater degree than the peak sodium current during an action potential. This is indeed the case (Fig. 7.3), and may explain why phenytoin affects burst behaviour to a greater extent than normal synaptic transmission [6].

Why is it that some people require higher serum levels of, or are resistant to, these drugs? Recently, a polymorphism in the *SCN1A* gene which affects the proportion of alternative channel transcripts (neonatal versus adult forms) has been shown to partially explain resistance to phenytoin and carbamazepine [7]. Since lamotrigine, carbamazepine and phenytoin act at the same site in similar fashions, we might expect epilepsy that is resistant to one of these drugs to be be resistant to the others. This does not seem to be the case. Sodium channels from patients with refractory temporal lobe epilepsy may be selectively resistant to carbamazepine [8]. Furthermore, drug resistance may be not only a pharmacodynamic phenomenon, but also a pharmacokinetic phenomenon, and there is some evidence of drug resistance being mediated by multidrug-resistant proteins that 'remove' drugs from the extracellular fluid and thus from their site of action [9].

The fact that the drugs have a similar mode of action could be an argument, in certain circumstances, for their concomitant use. So if seizures partially respond to one of these drugs, but further increases in dose are limited by side-effects, then the addition of a drug that acts at the same site, but has dissimilar side-effects, is likely to have an additional benefit: the effects would be infra-additive (i.e. the efficacy of the combination would be less than the combination of the efficacies). Do other antiepileptic drugs have effects on the sodium channel? Oxcarbazepine and eslicarbazepine probably have similar effects to carbamazepine [10,11]. Valproate seems to inhibit rapid repetitive firing [12], but acts at a different site from that at which carbamazepine, lamotrigine and phenytoin act. Phenobarbital and benzodiazepines may inhibit the sodium channel at high concentrations – concentrations that are not usual in clinical practice, but which may be attained during drug loading for the treatment of status epilepticus. The newer antiepileptic drugs – rufinamide, topiramate and zonisamide – also have actions on sodium channels, the exact nature and importance of which are unclear [13–15]. In addition to these three states of the sodium channel, there is also a slow inactivated state which occurs with sustained or repeated depolarizations. This state is selectively enhanced by the new antiepileptic drug lacosamide [16].

Calcium channels

Calcium channels are putative targets for antiepileptic drugs, although their importance in mediating antiepileptic effects is largely unknown (Table 7.2). The main pore-forming subunit of

Table 7.2 Action of antiepileptic drugs on calcium channels.

Anticonvulsant	Calcium ion channel			
	L-type	N-type	P/Q-type	T-type
Carbamazepine	*			
Ethosuximide				*
Fosphenytoin	*			*
Gabapentin	?		*	
Lamotrigine		*	?	
Levetiracetam		*	?	
Oxcarbazepine (MHD)			*	*
Phenobarbitone	*	*		*
Phenytoin	*			*
Topiramate	*	*		
Zonisamide				*

MHD, monohydroxy derivative.

calcium channels is similar in structure to that of sodium channels. This α_1-subunit is a 170- to 240-kDa protein, consisting of four homologous domains that each consist of six α-helical transmembrane segments. The pore-forming segments and the mechanism of inactivation are similar to that of the sodium channels [17]. Cloning has uncovered 10 subtypes of the α_1-subunit; these have been named $\alpha_{1A\text{-}I}$ and α_{1s} (this exists only in skeletal muscle), but have now been labelled $Ca_v1.1$–1.4 (L-type), $Ca_v2.1$–2.3 (P/Q-, N- and R-type) and $Ca_v3.1$–3.3 (T-type). In addition, there are associated subunits, $\alpha_2\delta$ and β, that promote channel expression and affect channel kinetics. A third auxiliary subunit, the γ-subunit, is expressed in skeletal muscle, but its expression and relevance in the brain are controversial [17].

In the brain four main classes of voltage-gated calcium channel are expressed: L-, P/Q-, N- and T-type channels [17]. L-, P/Q- and N-type channels are high-voltage-activated channels that require significant depolarization before activation, whilst the T-type channel is a low-voltage-activated channel and is activated at relatively hyperpolarized potentials.

The L-type channels are expressed mainly postsynaptically and are involved in postsynaptic calcium entry upon neuronal depolarization. L-type channels inactivate only slowly (long-lasting channels), thereby permitting sustained calcium entry [17]. L-type channels are typically blocked by dihydropyridines (e.g. nifedipine), and are regulated by protein phosphorylation and by calcium autoregulation [17]. Calcium entry through L-type channels is the major contributor of calcium to trigger the afterhyperpolarization (see below) in certain neuronal subtypes, particularly in the hippocampus, and the somatic expression of L-type channels means that they are ideally placed to open during the depolarization that occurs with an action potential. Calcium entering through L-type calcium channels may also have other effects, including gene regulation and the expression of long-term synaptic potentiation with strong stimulation. Blockade of L-type calcium channels has a variety of effects on epileptic discharges, and can have both anticonvulsant and proconvulsant effects, possibly by inhibiting synaptic potentiation, yet also inhibiting afterhyperpolarization. L-type calcium antagonists are proconvulsant in absence epilepsy models [18]. L-type antagonists may, however, inhibit epileptogenesis by inhibiting the calcium entry that secondarily activates various genes necessary for the epileptogenic process [19]. Some antiepileptic drugs have been proposed to antagonize L-type calcium channels, including carbamazepine [20], topiramate [21] and phenobarbital at high anaesthetic doses [22]. The relevance of this to their antiepileptic effect is difficult to predict, but this antagonism may contribute to their side-effects, including the pro-absence effect of carbamazepine.

N- and P/Q-type channels are expressed at synaptic boutons, where they mediate calcium entry necessary for neurotransmitter release. These channels are rapidly inactivating, resulting in brief calcium transients. This calcium entry then triggers exocytosis of the presynaptic vesicles. N- and P/Q-type channels are primarily regulated by G-proteins; they are thus modulated by G-protein-linked receptors such as $GABA_B$ receptors [17]. Inhibiting these calcium channels inhibits neurotransmitter release. The following antiepileptic drugs have been proposed to inhibit N-type calcium channels: lamotrigine [23,24], levetiracetam [25], phenobarbital at high doses [22] and topiramate [21]. Lamotrigine may also inhibit P-type channels [23], and levetiracetam has some effect on P- or P/Q-type channels [26]. Although only oxcarbazepine has some weak effect on L-type channels [27], the monohydroxy derivative (its main metabolite) inhibits high-voltage-activated calcium channels that are not L-type (presumably P/Q- or N-type channels) [28]. The effect of gabapentin and pregabalin on calcium channels is complex and novel; both show strong and specific binding for the $\alpha_2\delta$ auxiliary calcium channel subunit and may modulate P/Q-type calcium channels [29]. Gabapentin may also inhibit some peripheral L-type channels in a use-dependent manner, but the significance of this for the central nervous system is, at present, unknown [30].

T-type channels are activated at relatively hyperpolarized potentials. They open with small depolarization (low voltage activated), and then rapidly inactivate. T-type channels undoubtedly contribute to the generation of spike–wave discharges associated with absence epilepsy [31]. Hyperpolarization of thalamocortical cells results in the activation of T-type channels, which are then opened by the subsequent repolarization, leading to calcium entry that further depolarizes, leading to action potential generation. Spike activity in the thalamocortical neurones results in the recruitment of neocortical neurones which, via reticular thalamic neurones, inhibit and so hyperpolarize thalamocortical neurones (Fig. 7.4). Ethosuximide, an effective anti-absence drug, has been proposed to inhibit specifically T-type calcium channels [32]. This hypothesis has been challenged in a study that found that ethosuximide has no effect on calcium currents, but instead modulates neuronal bursting by decreasing the persistent sodium current, and perhaps the calcium-dependent potassium current [33]. More recent studies using cloned channels have, however, demonstrated that ethosuximide does inhibit T-type calcium channels at therapeutically relevant concentrations [34]. A possible explanation for these opposing findings is that ethosuximide binds to inactivated T-type channels. Since T-type channels are inactivated at depolarized potentials, then ethosuximide's efficacy is dependent on voltage and will show use dependence [34]. Thus, the inefficacy of ethosuximide at T-type channels found in one study [33] could be

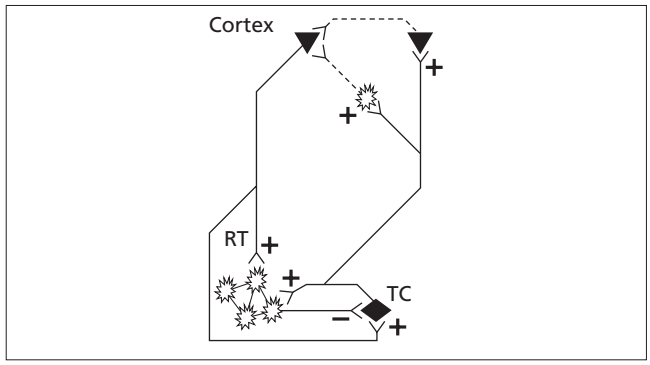

Fig. 7.4 The thalamocortical circuit proposed to underlie spike–wave discharges. RT, reticular thalamic neurones; TC, thalamocortical neurones. Filled, excitatory neurones; open, inhibitory neurones. RT hyperpolarize TC thus activating T-calcium currents that result, on depolarization, in burst firing and so excitation of cortical neurones. These in turn feedback onto RT and so the cycle continues.

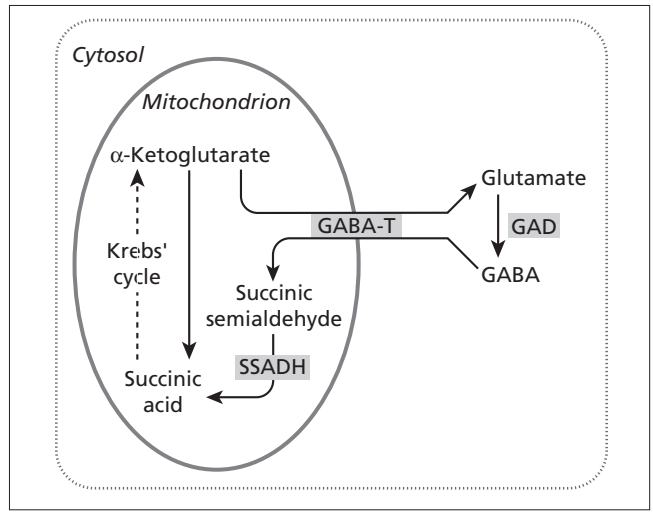

Fig. 7.5 GABA shunt. α-Ketoglutarate and succinic acid are two intermediaries in the Krebs' cycle within the mitochondria. Outside the mitochondria, glutamate is converted to GABA by glutamic acid decarboxylase (GAD). GABA is converted by GABA transaminase (a mitochondrial enzyme) into succinic semialdehyde and then by succinic semialdehyde dehydrogenase (SSADH) to succinic acid; α-ketoglutarate is converted in this reaction to glutamate.

explained by the relatively hyperpolarized potentials that were used (this would result in most T-type channels being in the active, ethosuximide-insensitive state) [34]. Nevertheless, ethosuximide's mode of action is probably more complex than just inhibition of T-type channels [33]. Zonisamide, another drug with anti-absence effects, has been found to inhibit T-type calcium channels [35]. T-type channels can be subdivided into three types, and the expression of these varies between brain regions [17]. Phenytoin and the barbiturates inhibit T-type currents in dorsal root ganglion (valproate has a weak effect), but have minimal effect on thalamic T-type currents [36]. Furthermore, the low-voltage-activated calcium current is not necessarily confined to T-type channels [37]. Thus, some of the effect of phenytoin on low-voltage-activated calcium currents in hippocampal neurones could be because of an effect of phenytoin on other calcium channel subtypes [33]. Some T-type channels may play a part in the bursting of 'epileptic' neurones in the hippocampus, and thus drugs that reduce these T-type channels could be effective in partial epilepsy [38].

GABA and GABA receptors

GABA is the major inhibitory neurotransmitter in the brain. It is formed and degraded in the GABA shunt (Fig. 7.5). Glutamic acid decarboxylase (GAD) converts glutamate to GABA. Promotion of GABA synthesis has been proposed to contribute to the action of some antiepileptic drugs, including valproate [39]. GABA is degraded by GABA transaminase to succinic semialdehyde; α-ketoglutarate accepts the amino group in this reaction to become glutamate (see Fig. 7.5). GABA is transported into vesicles by the vesicular transporter, VGAT, which has been cloned. As this transporter is absent from some GABAergic synapses, then other vesicular transporters probably also exist. GABA acts at three specific receptor types: $GABA_A$, $GABA_B$ and $GABA_C$ receptors. $GABA_C$ receptors are present almost exclusively within the retina, where they are responsible for fast chloride currents. $GABA_C$ receptors have a high affinity for GABA and slowly desensitize, possibly explaining their particular sensitivity of the retina to vigabatrin-induced damage.

$GABA_A$ receptors

$GABA_A$ receptors are expressed mainly postsynaptically within the brain (presynaptic $GABA_A$ receptors have been described within the spinal cord, and at specific synapses in the brain). They are heteropentameric channels constructed from five of at least 16 known mammalian subunits, grouped in seven classes: α, β, γ, δ, σ, ε and π. Each subunit has four transmembrane segments (termed M1–M4), with M2 contributing to the ion-conducting pore (Fig. 7.6). The large number of different subunits permits a large number of putative receptor isoforms, the most abundant in the brain being $GABA_A$ receptors composed of $\alpha_1\beta_2\gamma_2$ (see Fig. 7.6).

The subunit composition determines the specific effects of allosteric modulators of $GABA_A$ receptors, such as neurosteroids, zinc and benzodiazepines. The subunit composition also determines the kinetics of the receptors and can affect desensitization. Importantly, the subunit composition of $GABA_A$ receptors expressed in neurones can change during epileptogenesis, and these changes influence the pharmacodynamic response to drugs [40]. $GABA_A$ receptor activation results in the early rapid component of inhibitory transmission. Since $GABA_A$ receptors are permeable to chloride and, less so, bicarbonate, the effects of $GABA_A$ receptor activation on neuronal voltage are dependent on the chloride and bicarbonate concentration gradients across the membrane. In neurones from adult animals, the extracellular chloride concentration is higher than the intracellular concentration, resulting in the equilibrium potential of chloride being more negative than the resting potential. Thus, $GABA_A$ receptor activation results in an influx of chloride and cellular hyperpolarization. This chloride gradient is maintained by a membrane potassium/chloride co-transporter, KCC2 [41]. Absence of this transporter in immature neurones results in a more positive reversal potential for chloride, and thus $GABA_A$ receptor activation in these neurones produces

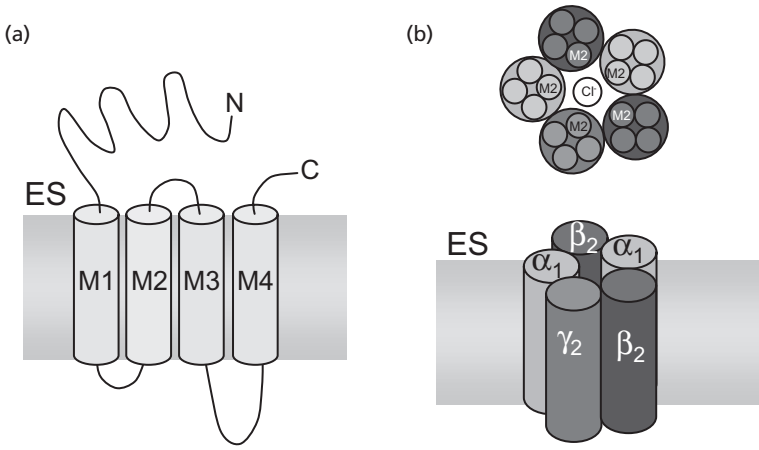

Fig. 7.6 The $GABA_A$ receptor. (a) Membrane topology of a single $GABA_A$ receptor subunit with four transmembrane segments (termed M1–4) and the extracellular NH_2 and COOH termini. M2 contributes to the ion-conducting pore. (b) Pentameric $GABA_A$ receptor composed of two α_1, two β_2, and one γ_2 subunits are the most abundant in the brain (bottom). A cross-section of the channel displays the Cl^- pore formed by M2 helical elements (top). ES, extracellular space.

neuronal depolarization [41]. During excessive $GABA_A$ receptor activation, intracellular chloride accumulation can result in depolarizing $GABA_A$ receptor-mediated responses. Repetitive stimulation can also have a further paradoxical effect in which the hyperpolarizing $GABA_A$ receptor-mediated potential is followed by a prolonged depolarizing potential. This depolarizing potential is partially mediated through an extracellular accumulation of potassium extruded by activation of KCC2 [42]. Thus, under certain circumstances, $GABA_A$ receptors can mediate excitation rather than inhibition. Drugs that inhibit carbonic anhydrase, such as acetazolamide, topiramate and zonisamide, will reduce the intracellular bicarbonate and thus can reduce these depolarizing GABA responses [43].

Benzodiazepines are specific modulators of $GABA_A$ receptors and act at $GABA_A$ receptors that contain an α_1, α_2, α_3 or α_5-subunit in combination with a γ-subunit [44]. Drugs acting at the benzodiazepine site have different affinities for the different α-subunit-containing $GABA_A$ receptors, and this specificity can affect pharmacodynamic response [45]. This is perhaps because of the varied distribution of these receptors in the brain. Thus, α_1-subunit-containing receptors seems to have mainly a sedative effect, and this is perhaps responsible for this side-effect of benzodiazepines [45]. This also explains why zolpidem, a drug that has great affinity for $GABA_A$ receptors containing the α_1-subunit, has marked sedative effects and weak anticonvulsant efficacy [46]. More selective ligands could thus result in benzodiazepine agonists that have a less sedative effect and a greater anticonvulsant potential. The benzodiazepines' main effect is to increase the affinity of $GABA_A$ receptors for GABA, and to increase the probability of receptor opening [47]. Barbiturates are less selective than benzodiazepines, and potentiate $GABA_A$ receptor-mediated currents. The potentiation is partly mediated by prolonging receptor opening times [47,48]. Stiripentol may have a similar mechanism of action [49]. In addition, at high concentrations, barbiturates can directly activate the $GABA_A$ receptor [44]. This partly explains their anaesthetic effect at high concentrations. Other anaesthetic agents, such as propofol, have similar effects on $GABA_A$ receptors [44]. Topiramate can also potentiate $GABA_A$ receptors by an unknown mechanism [50].

$GABA_A$ receptors have other modulatory sites, and can be modulated by zinc [44]. In hippocampi from epileptic brains, $GABA_A$ receptor function is more sensitive to allosteric inhibition by zinc. This zinc-induced inhibition of $GABA_A$ receptors, as well as of glycine receptors, was fully reversed on acute application of levetiracetam in cultured hippocampal neurones [51]. Levetiracetam also prevented the rundown of $GABA_A$ receptor currents in hippocampal tissue from patients with epilepsy following repeated GABA application [52]. Neurosteroids can also modulate $GABA_A$ receptors [44], and variations in neurosteroid levels may explain why seizures occasionally cluster around the time of menstruation [53]. Ganaxolone, a neurosteroid, was, nevertheless, dropped from clinical trials due to lack of efficacy [54].

On occasion, $GABA_A$ receptor agonists can have paradoxical proepileptic effects, perhaps as a result of GABA being excitatory in some circumstances (see above), synchronization of neurones through the interneuronal network or preferential potentiation of GABAergic inhibition of GABAergic interneurones leading to paradoxical disinhibition. $GABA_A$ receptor agonists can also exacerbate absence seizures. Absence seizures are generated within a recurrent loop between the thalamus and neocortex, and their generation is dependent upon oscillatory behaviour mediated by $GABA_A$ receptors, $GABA_B$ receptors, T-type calcium channels and glutamate receptors [55]. One hypothesis is that hyperpolarization of the thalamocortical neurones in the thalamus mediated by GABAergic inhibition leads to activation of T-type calcium currents which open on neuronal depolarization, resulting in repetitive spiking. This activates neurones in the neocortex, which in turn stimulate the thalamic reticular nucleus, leading to GABAergic inhibition of the thalamocortical (relay) neurones (see Fig. 7.4), and so the cycle continues [55]. Within this circuit, clonazepam preferentially inhibits the thalamic reticular neurones, perhaps due to the higher expression of α_3-containing $GABA_A$ receptors [56]. Non-specific $GABA_A$ receptor agonists, $GABA_B$ receptor agonists or agonists of specific $GABA_A$ receptors can all hyperpolarize thalamocortical neurones and so can have a pro-absence effect. This also occurs through the potentiation of GABAergic inhibition with ganaxalone [57].

$GABA_B$ receptors

$GABA_B$ receptors are expressed both pre- and postsynaptically. They are G-protein-coupled receptors, and consist of dimers of either $GABA_{B1a}$ or $GABA_{B1b}$ and $GABA_{B2}$ subunits. Activation of $GABA_B$ receptors results in inhibition of adenylyl cyclase, inhibition of voltage-gated calcium channels and activation of G-protein-linked inwardly rectifying potassium channels (GIRKs). The postsynaptic effect is a prolonged hyperpolarization leading to the late component of inhibitory neurotransmission. At many synapses, postsynaptic $GABA_B$ receptors are located far from the release site, and are activated only by GABA spillover during simultaneous release of GABA from multiple synapses [58]. Although the effects of this would be to decrease the excitability of the system, $GABA_B$ receptor activation may enhance the oscillatory nature of certain structures [58]. Indeed, activation of postsynaptic $GABA_B$ receptors in the thalamus has been proposed to underlie the generation of absence seizures. The presynaptic effect of $GABA_B$ receptors is not only to inhibit GABA release at inhibitory synapses as a process of autoregulation, but also to inhibit glutamate release at excitatory synapses, and thus the effect on the network is complex and difficult to predict. Results with $GABA_B$ receptor agonists have been variable, but they seem to have a pro-absence effect; conversely, $GABA_B$ receptor antagonists have anti-absence effects but can be proconvulsant in other seizure models [59].

GABA uptake and breakdown

Other means of positively modulating GABAergic activity are to inhibit GABA uptake or inhibit GABA breakdown. GABA is mainly metabolized by GABA transaminase to succinic semialdehyde; glutamate is synthesized in this reaction (see above). Vigabatrin irreversibly inhibits GABA transaminase. This results in an increase in intracellular GABA that can produce an increase in vesicular GABA, and so inhibit transmission [60]. In addition, vigabatrin results in an increase in extracellular GABA that can be partly explained by decreased GABA uptake [61]. GABA released into the extracellular space is transported into neurones and glial cells via Na^+/Cl^--coupled GABA transporters (GAT) that can transport GABA against an osmotic gradient [62]. In human and rat, four GAT proteins have been identified and cloned: GAT-1, GAT-2, GAT-3 and BGT-1 [62]. GAT-1 is predominantly present on presynaptic GABAergic terminals and glia, and is the most prevalent GABA transporter in the rat forebrain. In contrast, GAT-3 is localized exclusively to astrocytes and glia, and GAT-2 has a more diffuse distribution. GABA uptake and GAT expression change during development, and are also regulated by protein kinase C (activated by a variety of G-protein receptors), a direct effect of GABA and tyrosine phosphatase [62].

Amongst the most potent of GABA transporter inhibitors is nipecotic acid. Nipecotic acid proved to be a useful tool *in vitro*, but had poor penetration across the blood–brain barrier [63]. Nipecotic acid was thus effective in animal epilepsy models only if it was administered intracerebrally. In order to improve the blood–brain penetration of nipecotic acid and similar compounds, a lipophilic side chain was linked to them via an aliphatic chain. This markedly increased the potency and the specificity of these compounds for the GAT-1 transporter as well as increasing brain penetration [64]. These compounds, in contrast to nipecotic acid, are not substrates for the transporter [65]. One such compound, tiagabine (*R*-[–]-1-[4,4-*bis*(3-methyl-2-thenyl)-3-butenyl]-3-piperidinecarboxylic acid), was selected because of its good preclinical profile. Tiagabine is thus a GAT-1-specific, non-transportable, lipid-soluble GABA uptake inhibitor.

Microdialysis studies have demonstrated an increase in extracellular brain GABA concentrations in various brain regions following systemic or local administration of tiagabine [66,67]. There does, however, appear to be significant differences in the effect of tiagabine on extracellular GABA between brain areas, perhaps secondary to different levels and expression of the different GATs. Thus, the thalamus seems to be less sensitive to the effects of tiagabine than the hippocampus [66]; indeed, the dose of tiagabine that results in an increase in thalamic GABA is much higher than that necessary to mediate an antiepileptic effect and is of a magnitude that has a possible proconvulsive effect [67]. Tiagabine, in contrast to vigabatrin, has no effect on total brain GABA. This and the failure of tiagabine to accumulate in the retina, again in contrast to vigabatrin, may mean that tiagabine will not cause the concentric visual field defects associated with vigabatrin [68].

Although many explanations of vigabatrin's and tiagabine's mode of action concentrate on raising the extracellular GABA concentration, these drugs have other important effects. The time-course of the GABA transit in the synaptic cleft is partly (and variably) determined by GABA uptake; tiagabine can thus prolong the synaptic GABA transient. In addition, by decreasing GABA uptake there is greater spillover of GABA from the synaptic cleft onto extrasynaptic receptors. Each of these mechanisms can have an effect on inhibition, and there is no consensus as to the relative importance of each.

Increasing extracellular GABA can have two opposing effects. Extrasynaptic $GABA_A$ receptors have a high affinity and less propensity to desensitize. Extracellular GABA acting at these receptors can mediate a tonic (continuous) form of inhibition. Such inhibition is developmentally regulated and demonstrates regional and cellular specificity [69]. Since extracellular GABA concentrations can vary and increase during seizures, such tonic inhibition would be expected to demonstrate similar increases during seizure activity. A second effect of increasing extracellular GABA is to desensitize synaptic $GABA_A$ receptors [70]. This can result in smaller amplitude $GABA_A$ receptor-mediated currents [70]. Thus, vigabatrin increases tonic inhibition, but decreases synaptically mediated inhibition (Fig. 7.7) [70].

The effects of inhibiting GABA uptake on the time-course of GABA in the synaptic cleft are dependent upon the extent to which the time-course is governed by uptake as opposed to just diffusion, and is thus dependent upon the affinity, on-rate and density of GABA transporters and the geometry of the cleft and the extracellular space. GABA uptake varies with age and location. Inhibiting GABA uptake has no effect on inhibitory postsynaptic current (IPSC) kinetics at early ages, whilst prolonging IPSCs at later age groups [71]. The effect of changing the time-course of the GABA transient is not immediately predictable. Importantly, at some synapses the decay of the $GABA_A$ receptor-mediated IPSC/P is determined mainly by the spatiotemporal profile of the GABA concentration rather than the kinetics of the $GABA_A$ receptors [72]. At these synapses, prolonging the

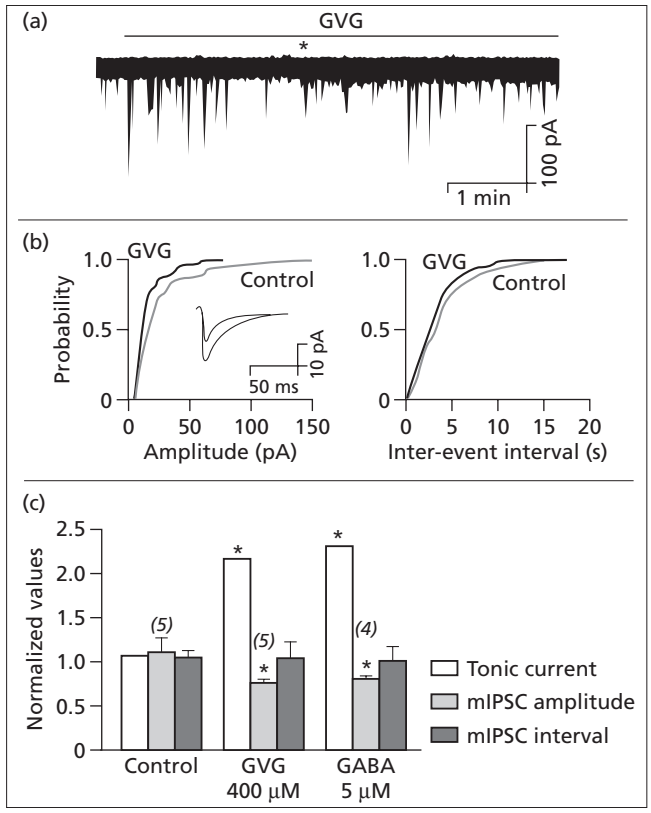

Fig. 7.7 Acute vigabatrin (GVG) or GABAs reduces miniature inhibitory postsynaptic currents (pIPSC) amplitude, but increases tonic inhibition. (a) GVG (400 μmol) applied to an untreated slice produced an increase in tonic current that was apparent after a couple of minutes (*) and increased gradually throughout the experiment. (b) GVG reduced the mIPSC amplitude in all cases, without affecting the interevent interval. (c) The tonic current was increased by GVG or GABA (experiments performed with $GABA_B$ receptors blocked). From ref. 70.

time-course of the synaptic GABA transient prolongs the duration of the IPSC/P [72]. This results in an effect on the current that is similar to benzodiazepines or barbiturates, although mechanistically different. In contrast, studies at other synapses and in different neurones have found no change in the decay of miniature IPSP/Cs (or even small IPSP/Cs) with block of GABA uptake, but have found a prolongation of large-amplitude IPSCs [73,74]. Blockade of GABA uptake in large evoked IPSC/Ps affects the late, but not early, decay. The discrepancy between the effects on miniature IPSC/Ps compared with large-amplitude IPSC/Ps can be explained by hypothesizing that the decay of small IPSC/Ps and the initial decay of the IPSC/P are determined by single-channel kinetics and/or diffusion from the cleft [74]. Release of GABA from many sites, however, can result in spillover to GABA receptors beyond the activated synapses, and this spillover is enhanced by a decrease in GABA uptake [73]. Spillover of neurotransmitter can activate not only extrasynaptic $GABA_A$ receptors but also $GABA_B$ receptors, which also lie outside the synaptic cleft [73]. Indeed, despite the presence of postsynaptic $GABA_B$ receptors, GABA released by a single interneurone usually activates postsynaptic $GABA_A$ receptors alone (Fig. 7.8) [58]; spontaneous IPSCs typically lack a $GABA_B$ receptor-mediated component [75]. Synchronous release of GABA from several interneurones, such as occurs with either strong stimulation or synchronous neuronal activity, can, however, activate postsynaptic $GABA_B$ receptors [58,73]. Blocking GABA uptake results in activation of $GABA_B$ receptors by GABA released by even a single interneurone (see Fig. 7.8) [58]. Thus, blocking GABA uptake can result in an enhancement of postsynaptic $GABA_B$ receptor-mediated inhibition. A defect in GABA uptake has been hypothesized to be the substrate for genetic absence epilepsy in one rat model [76]. It is thus not surprising that tiagabine and vigabatrin can worsen absence seizures, and can induce absence status epilepticus in humans [77]. Enhancement of $GABA_B$ receptor activation will have not only a postsynaptic effect, but also a presynaptic effect, and will decrease the release of GABA from GABAergic terminals (decreasing inhibition), and glutamate from glutamatergic terminals (decreasing excitation). The overall effect on the network is thus difficult to predict.

Repetitive stimulation and bursts of neuronal activity such as occur during seizure activity can both cause $GABA_A$ receptor-mediated depolarizing responses (see above), and these could potentiate rather than inhibit epileptic activity. Tiagabine potentiates these depolarizing responses [78], and thus the concern is that, through this mechanism, tiagabine could in some circumstances enhance seizure activity.

Other targets

Glutamate and glutamate receptors

Glutamate is a non-essential amino acid that does not cross the blood–brain barrier but is readily synthesized by various biochemical pathways from different precursors including α-ketoglutarate (an intermediate of the Krebs' cycle), glutamine, ornithine and proline. GABA transaminase contributes to the synthesis of glutamate (see Fig. 7.5). Thus vigabatrin, which inhibits GABA transaminase as well as inhibiting the breakdown of GABA, may also decrease the synthesis of glutamate [79]. Glutamate is present in abundance in brain tissue, and is the major excitatory transmitter in the central nervous system. Glutamate is transported into vesicles by a specific vesicular transporter, and exhaustion of vesicular glutamate has been proposed to be a possible mechanism of seizure termination. Abnormalities of glutamate uptake have been hypothesized to contribute to seizure generation, and thus drugs that modulate glutamate uptake may have an antiepileptic effect. Glutamate is present in the brain in large concentrations (10 mmol), but this is predominantly intracellular glutamate [80]. The extracellular glutamate is maintained at concentrations 5000 times lower than this (approximately 2 μmol) by high-affinity glutamate uptake into predominantly glia. Glutamate acts at three distinct receptor types: NMDA, non-NMDA [consisting of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA)- and kainic acid (KA)-sensitive receptors] and metabotropic glutamate receptors. These receptor subtypes have very different properties (Table 7.3).

AMPA and kainate receptors

Non-NMDA receptors are mainly associated with channels that are permeable to sodium ions, and are responsible for fast excit-

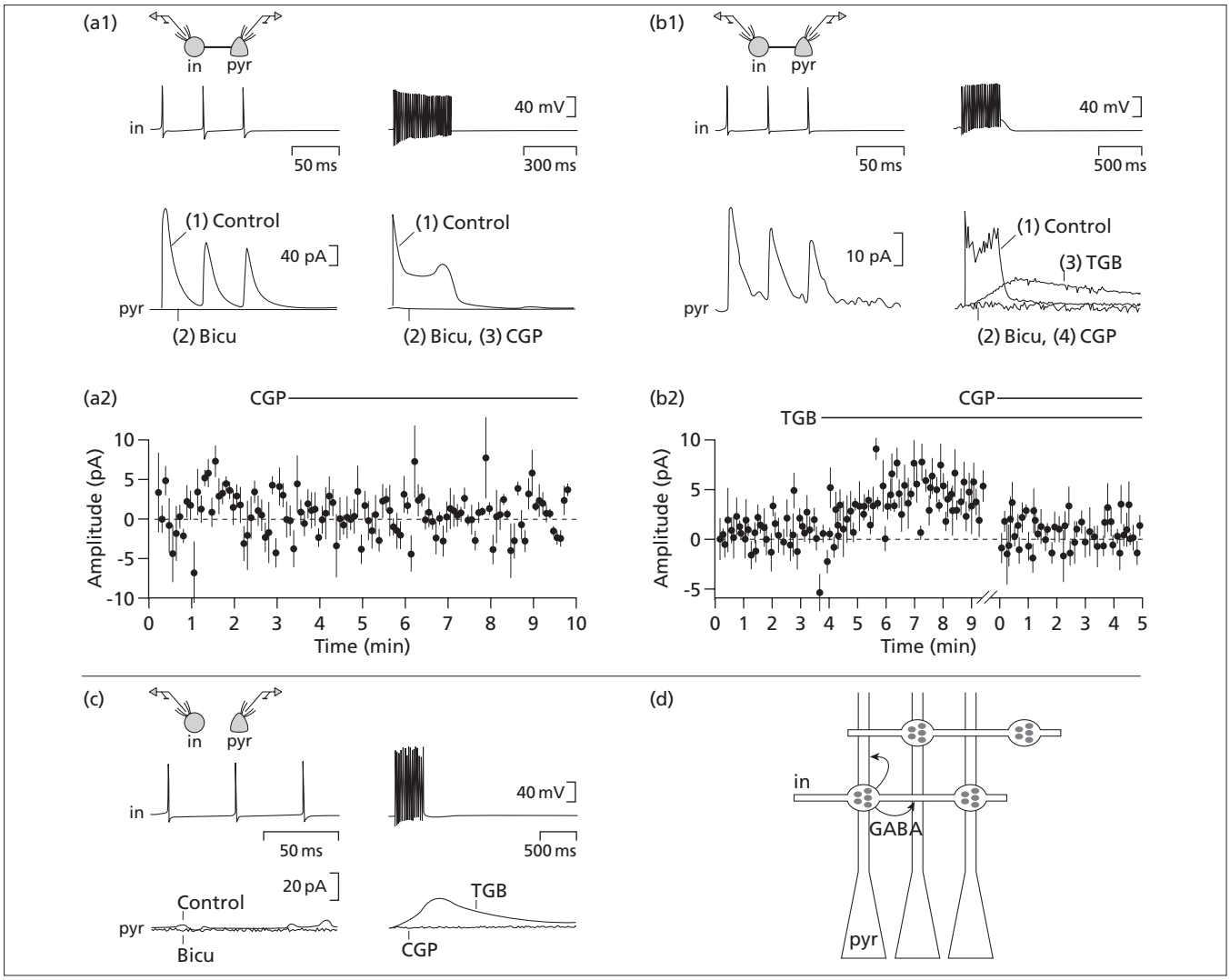

Fig. 7.8 Activation of $GABA_B$Rs by release of GABA from a single interneurone. (a1) Dual recording from a connected interneurone/pyramidal cell (in/pyr) pair. Three action potentials triggered in the interneurone elicit three inhibitory postsynaptic currents in the pyramidal cell. A train of action potentials (100 Hz) from the interneurone elicits an outward current in the pyramidal cell. Both types of responses are completely blocked by the $GABA_A$R antagonist bicuculline. Addition of the $GABA_B$R antagonist CGP62349 (2 μmol) has no further effect. (a2) Summary graph of the time-course of the amplitude of the response, after application of bicuculline, for eight experiments. (b1) Similar experiment to that illustrated in (a1), with the difference that the GABA uptake-blocker tiagabine (TGB; 10 μmol) was applied after perfusion of bicuculline. Under these conditions, the AP train elicits a long-lasting outward current, which is abolished by CGP62349. (b2) Summary graph of the time-course of the amplitude of the response, after application of bicuculline, for six experiments. (c) Dual recording from a non-connected in/pyr cell pair. After application of tiagabine, a train of APs in the interneurone elicits an outward current that can be blocked by CGP62349. (d) Schematic diagram illustrating extrasynaptic $GABA_B$R activation by diffusion of GABA on both postsynaptic and neighbouring pyramidal cells. From ref. 58.

Table 7.3 Properties of ion channel-associated glutamate receptors.

	Non-NMDA receptors		
	Kainate	AMPA	NMDA receptors
Subunits	GluR5	GluR1	NR1
	GluR6	GluR2	NR2A
	GluR7	GluR3	NR2B
	KA1	GluR4	NR2C
	KA2	–	NR2D
	–	–	NR3
Associated ion conductance	–	Na^+ (Ca^{2+} for AMPA receptors lacking the GluR2 subunit)	Ca^{2+}, Na^+
EC_{50} for glutamate	–	500 μmol	2–3 μmol

atory neurotransmission. The receptors consist of four subunits; receptors comprising GluR1–4 subunits are the AMPA receptors, and those comprising GluR5–7 and KA1–2 are the kainate receptors [81]. AMPA receptors lacking the GluR2 component are also permeable to calcium ions. Relatively large concentrations of glutamate result in channel opening and a rapid depolarization. The concentration that gives half the maximum response (EC_{50}) for AMPA receptors is of the order of 500 μmol of glutamate [82]. AMPA receptors are putative targets for antiepileptic drugs. Since AMPA receptors mediate most excitatory transmission in the brain, drugs acting at these receptors are likely to have physiological consequences. Nevertheless, topiramate at high concentrations acts at AMPA/kainate receptors [83]; whether this

is responsible for its antiepileptic effect or dose-related side-effects is unknown. Levetiracetam also inhibits AMPA receptor currents at clinically relevant concentrations, which may partially explain its antiepileptic action [84]. There are other drugs in clinical trials, such as talampanel, that are AMPA receptor antagonists [85]. Kainate receptors, as well as having a postsynaptic role in exciting interneurones and principal cells, are also present presynaptically [86]. These presynaptic receptors can increase or decrease neurotransmitter release depending on subtype and target. In addition, axonal kainate receptors can affect axonal excitability, leading to ectopic action potentials [87]. It is thus difficult to predict whether the effect of kainate receptor activation would be pro- or anti-ictogenic [88]. The agonist KA is, however, a powerful convulsant, thus kainate antagonists would perhaps be expected to have antiseizure effects [88]. Of interest is that interneurones may express a different kainate receptor subtype from that expressed on principal cells, raising the possibility that kainate receptor subtype-specific agonists and antagonists may provide a powerful approach to modulate the excitability of the system [88]. Indeed, there has been a report of a GluR5-specific antagonist with antiepileptic effects in pilocarpine-induced seizures [89], yet there is a separate study demonstrating that GluR5 agonists can be antiepileptic [90]. This dichotomy demonstrates the difficulties in predicting the effects of kainate receptor antagonists and agonists.

NMDA receptors

NMDA receptors are associated with channels that are permeable to calcium and sodium ions. NMDA receptors are composed of multiple NR1 subunits in combination with at least one subtype of NR2 subunit (NR2A, B, C or D) and occasionally NR3 subunit. The receptor has high-affinity sites for both glycine and glutamate as well as sites for polyamines and zinc. Relatively low concentrations of glutamate are necessary to activate the receptor. NMDA receptors typically have an EC_{50} for peak response of the order of 2–3 μmol of glutamate (i.e. orders of magnitude lower than that of AMPA receptors) [82]. NMDA receptors are thus influenced by the ambient glutamate concentration and can be activated extrasynaptically by glutamate spillover during excessive synaptic activity such as occurs during seizures. NMDA receptor responses decay slowly, leading to a persistent depolarization that lasts for hundreds of milliseconds [91] and which can thus contribute to burst firing. NMDA activation by glutamate does not necessarily result in any detectable current flow, because at negative potentials the ionic pore is tonically blocked by magnesium. This block is released by depolarization. During normal synaptic activity, the time-course of the non-NMDA excitatory postsynaptic potential (EPSP) is substantially shorter than the latency for NMDA receptor activation. Even if activation of non-NMDA receptors should result in a sufficient depolarization to release the magnesium block, by the time most NMDA receptors are activated by glutamate, most neurones will have repolarized to such an extent that the magnesium block will be in place and no current will flow through the NMDA receptors [91]. If, however, the NMDA receptor activation coincides with neuronal depolarization, then the resultant depolarization will result in removal of the magnesium block and the channel will open and current will flow. The NMDA receptor thus acts as a coincidence detector. The resultant influx of calcium through NMDA receptors has secondary consequences, affecting the phosphorylation of proteins that can produce long-term synaptic potentiation, modulation of other receptors and, if excessive, even cell death. NMDA receptors would seem an ideal target for antiepileptic drugs, to prevent burst firing, proepileptogenic synaptic plasticity and neuronal death during prolonged epileptic activity (i.e. status epilepticus).

NMDA receptors, however, have numerous physiological roles in learning and motor control. This has meant that many of the NMDA receptor antagonists tried in epilepsy or for neuroprotection have had unacceptable side-effects. Interestingly, the adverse effects associated with NMDA receptor antagonists may be more prevalent in people with epilepsy, perhaps due to receptor modifications that occur with epileptogenesis. Nevertheless, some presently available antiepileptic drugs may have modulatory effects on NMDA receptors. NMDA receptors have binding sites not only for glutamate, but also for zinc, glycine and polyamines. These sites modulate receptor function by affecting rates of desensitization, affinity for glutamate and channel opening. The glycine site has also been proposed to be essential for NMDA receptor activation. Thus, felbamate, a drug that acts at the glycine site of the NMDA receptor, modulates NMDA receptor function [92]. Remacemide and its des-glycine metabolite may have a variety of effects on the NMDA receptor, acting both as channel blockers and as modulators [93]. NMDA receptors can also be modulated by other factors, such as pH, redox state and phosphorylation, that may provide additional drug targets. In addition, drugs that influence glutamate uptake can affect NMDA receptor activation, and so could possess antiepileptic activity [94].

Metabotropic glutamate receptors

Metabotropic glutamate receptors are G-protein-linked receptors that can be classified into three groups. Group I receptors are mainly expressed postsynaptically, where they enhance postsynaptic calcium entry, calcium release from internal stores and depolarization through inhibition of potassium currents. Group I receptors may thus play a part in neurodegeneration. Group I antagonists have neuroprotective and antiepileptic potential [95]. Presynaptic group I receptors can enhance neurotransmitter release. In contrast, presynaptic group II and group III metabotropic glutamate receptors inhibit both GABA and glutamate release. The selectivity of some group II receptors for GABA synapses onto interneurones results in agonists inhibiting the inhibition of interneurones (i.e. decreasing the excitability of the system). Indeed group II and group III agonists have had antiepileptic effects in genetic epilepsy models and kindling [96–99], and may prove useful as antiepileptic drugs.

Potassium channels

Potassium channels form one of the most diverse groups of ion channels. There are persistent potassium currents that determine the resting potential of neurones, but there are, in addition, other voltage-gated potassium channels with varying functions. The voltage-gated potassium channels influence the resting potential and thus the excitability of neurones. They also repolarize neurones following action potentials, and so partly determine action

potential width – a factor that can influence transmitter release. In addition, the rate of inactivation of potassium channels, which are activated during an action potential, influences the propensity for rapid repetitive firing. Voltage-gated potassium channels are thus critical for determining neuronal excitability.

Voltage-gated channels are assembled from four α-subunits, and the diversity of possible α-subunits leads to a multitude of combinations with different properties. The α-subunits vary in size; the largest have six transmembrane segments (similar to a single domain of the sodium and calcium channels). Analogous to sodium channels, the voltage-sensing segment is S4 and the pore is composed of S5 and S6; in contrast to sodium channels, the mechanism of fast inactivation depends on an N-terminal structure that, like a ball and chain, occludes the pore. There is also a slower form of inactivation, which is poorly understood. There are smaller α-subunits, which consist of two transmembrane segments that make up the inward rectifying potassium channels. Auxiliary β-subunits can also combine with the α-subunits and can influence channel kinetics and possibly receptor expression.

Conventionally, the voltage-gated potassium channels in the brain can be divided into channels that rapidly activate and inactivate (A-type channels), and channels that open upon depolarization but do not significantly inactivate (delayed rectifier channels). There are also potassium channels that close upon depolarization but are open at the resting potential (inward rectifying channels); these channels do not inactivate in the same fashion as the other voltage-gated potassium channels, but the channels are rather blocked by internal ions at depolarized potentials. There are a variety of inward rectifying channels: some are G-protein linked and are opened by activation of G-protein-linked receptors (e.g. $GABA_B$ receptors), whilst some are opened by rises in intracellular adenosine triphosphate (ATP). There are other potassium channels that are similar in structure to the voltage-gated potassium channel, but are opened by intracellular calcium (calcium-activated potassium channels that mediate the afterhyperpolarization) or by cyclic nucleotides (mainly present in the retina, where they mediate photoreceptor responses). There are also specific potassium channels that are inactivated by acetylcholine – termed M-type channels.

Although modulation of potassium channels would seem to be an ideal target for antiepileptic drugs, most drugs have no or poorly characterized effects on potassium channels. Phenytoin and levetiracetam may selectively block delayed rectifier potassium channels [100,101]; this inhibition could prolong the action potential duration, thereby prolonging the 'refractory period', resulting in a reduction of sustained repetitive firing. Indeed, at lower firing frequencies, such an effect may be proconvulsant; a longer action potential at the presynaptic terminal could increase the calcium influx, thereby enhancing neurotransmitter release. Drugs that potentiate potassium channels would be expected to have an antiepileptic effect by decreasing the excitability of neurones. Potentiation of specific potassium channels has indeed been proposed to contribute to the action of some presently available antiepileptic drugs. Thus, gabapentin potentiates ATP-activated inward-rectifying potassium channels [102], and topiramate and acetazolamide induce a membrane hyperpolarization that is blocked by the potassium channel blocker, barium [43]. The afterhyperpolarization induced by calcium-dependent potassium channels also reduces neuronal excitability, and ethosuximide may mediate some of its effect by potentiating such channels [33].

Retigabine, a putative antiepileptic drug, has as perhaps its main mode of action potentiation of potassium channels. Retigabine induces a hyperpolarizing shift in the activation curves of KCNQ2/3 channels and probably other potassium channels from the same family that are responsible for the M current in neurones [103]. Interestingly, mutations of KCNQ2/3 are responsible for benign neonatal seizures. The extent to which other antiepileptic drugs affect potassium channels remains unknown, but it is likely that modulation of potassium channels will be a future target for antiepileptic drug development.

Cyclic nucleotide-gated channels

The importance of hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels in epilepsy has only recently been recognized. Their structure resembles those of Shaker K^+ channels: each HCN subunit consists of six transmembrane segments with a positively charged segment S4 serving as voltage sensor and an ion conduction pore between segment S5 and S6. Four subunits are thought to assemble to one homo- or heteromeric channel. There are four separate genes encoding biophysically distinct subunits termed HCN1–4. HCN channels are ubiquitously present in the brain with predominant expression of the HCN1, 2 and 4 subunits. The expression patterns substantially vary in different brain regions, e.g. the thalamus exhibits high expression of the 'slow activating' subunits HCN2 and 4, whereas hippocampal CA1 pyramidal neurones mainly express the 'fast activating' HCN1 subunit together with HCN2. Moreover, HCN channels also display distinct subcellular expression pattern, for example in CA1 pyramidal neurones they are expressed at a higher density in distal dendrites than in the somatodendritic membrane. Their functions depend on their subcellular localization and the HCN subunits expressed.

Cyclic nucleotide-gated channels underlie the H-current, which is different from other voltage-gated ion currents in many features. The H-current is a mixed inward current, carried by Na^+ and K^+ ions, that develops slowly upon hyperpolarization to below –60 mV. Conversely, it slowly deactivates upon depolarization. H-currents are directly enhanced by the second messenger, cAMP, the binding of which shifts the voltage-dependent activation curve to more depolarized potentials, so that more HCN channels are open at a given membrane potential. In the hippocampus and neocortex, H-currents contribute to the resting membrane potential, and to the integration of synaptic and somatic integration by partially setting the neuronal input resistance. The latter determines the neuron's sensitivity to incoming signals, as the H-current shunts the dendritic currents. In the thalamus, H-currents serve as the classical 'pacemaker' currents and generate, together with T-type calcium currents, physiological oscillations [31].

A down-regulation of dendritic H-currents has been suggested to be a proepileptic in animal models of chronic partial epilepsy (pilocarpine model, kainate model), whereas an up-regulation has been considered as a compensatory antiepileptic effect (e.g. in the hippocampal dentate gyrus of pilocarpine model and in patients

with mesial temporal lobe epilepsy) [104]. In absence seizures and the related thalamocortical loop, region-specific changes in HCN expression patterns were observed that may disturb the subtle interactions within this circuit, thereby favouring onset of spike–wave discharges and absences [105].

Cyclic nucleotide-gated channels are considered potential targets for antiepileptic drug therapy. Indeed, H-currents are enhanced by acetazolamide, gabapentin and lamotrigine [106–108]. Lamotrigine shifts the activation curve to more depolarized potentials, whereas gabapentin probably directly increases HCN channel conductance. Acetazolamide indirectly enhances H-currents via intracellular alkalinization. Increasing the H-current may have two potentially antiepileptic effects. In the hippocampus it would inhibit excitatory transmission to the soma and decrease excitability, so perhaps contributing to the efficacy of acetazolamide, gabapentin and lamotrigine in partial epilepsy. In the thalamus, it would depolarize thalamocortical neurones and so inhibit or terminate spike–wave discharges, possibly explaining the efficacy of acetazolamide, and lamotrigine against absence seizures. The role of HCN channels is, however, not clear-cut as pentobarbital has been reported to decrease, while the pro-absence drug gabapentin has been reported to increase, the H-current [109]. These apparent inconsistencies could be explained by the multiple targets of the drugs.

Synaptic vesicle protein SV2A

Synaptic vesicle fusion that precedes neurotransmitter release is a complex process involving a variety of proteins. Levetiracetam binds to one of these, the synaptic vesicle protein SV2A [110]. Binding does not occur to the two isoforms SV2B or SV2C. Importantly, in different animal models of epilepsy, the antiepileptic potency of levetiracetam and its derivatives positively correlated with their SV2A binding affinity (Fig. 7.9) [111]. This, and the fact that SV2A knockout mice strains display a severe seizure phenotype, strongly suggest that levetiracetam binding to SV2A is involved in its antiepileptic effect. SV2A is a glycoprotein with 12 transmembrane regions, a cytosolic N and C terminus, a long cytosolic loop and a long intravesicular loop that is glycosylated. Unfortunately, to date, the specific binding site of levetiracetam on the SV2A protein has not been reported. The function of SV2A is still unclear, and SV2A may regulate presynaptic calcium levels and also supports GABAergic and excitatory neurotransmission. Although SV2A has been identified as a specific binding site for levetiracetam, exactly how the drug exerts its antiepileptic effect and what changes in synaptic transmission occur is unknown.

Monoamines

It has been well established that monoamines play an integral role in epileptic phenomena. Experiments carried out in excised epi-

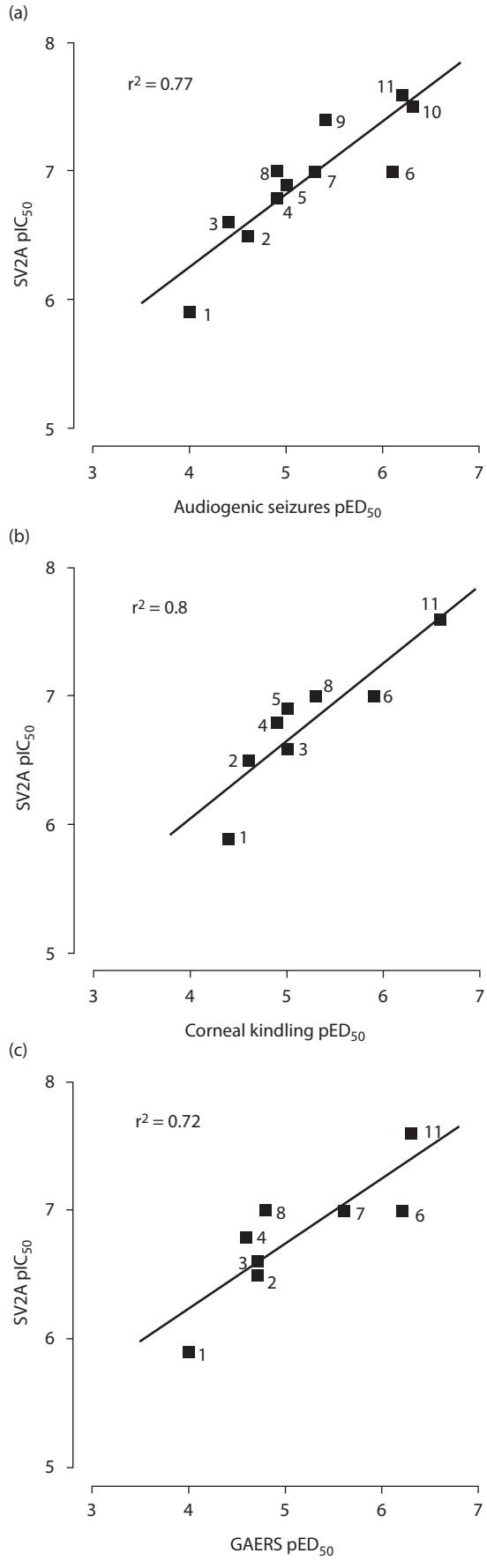

Fig. 7.9 Correlation between binding affinity and anticonvulsant potency of SV2A ligands against audiogenic seizures. (a) Corneal kindling (as a model for partial seizures). (b) Absence seizures (genetic absence epilepsy rats from Strasbourg; GAERS). (c) SV2A binding affinities (expressed as pIC_{50}) were measured in rat brain membranes with the use of [^{3}H]ucb 30889. Anticonvulsant potencies, based on dose–response studies, are shown as pED_{50}. Reprinted from ref. 111 with permission from Elsevier.

leptic brain tissue have shown alterations in both catecholaminergic and indoleaminergic activity when compared with non-epileptic tissue. In addition, monoamine content has been shown to differ in the cerebrospinal fluid of epileptic patients compared with non-epileptic patients [112]. Indeed, experimentally induced attenuation of monoamine content has been directly implicated in the onset and propagation of many seizure disorders [113,114] whereas experimentally induced accretion of monoaminergic activity has been shown to retard the development of epileptiform activity [115,116]. The role of GABA in the epilepsies has been well characterized but little is known of the input that other monoamines have to play in, or following, seizure generation.

Dopamine

It is generally accepted that alterations in central dopamine levels are responsible, in part, for the onset and continuance of many seizure disorders (see ref. 117 for a review). In the midbrain, inhibition of the substantia nigra (SN) has been shown to attenuate seizures in many animal models of seizure disorders. The SN projects dopaminergic neurones to the caudate putamen and, in turn, receives GABAergic afferents from the caudate putamen via one of two pathways. The first pathway, commonly known as the direct pathway, offers a direct monosynaptic GABAergic projection from the caudate putamen to the SN. The second pathway (indirect pathway) involves a GABAergic projection from the caudate putamen to the lateral globus pallidus. The globus pallidus then projects GABAergic efferents to the subthalamic nucleus that finally exerts glutamatergic tone onto the SN.

The SN and the caudate putamen have been thought to play major roles in the interruption and triggering of seizure generation, respectively. Seizure control appears to be partly regulated by the direct pathway and its ability to potentiate GABAergic activity within the SN. The antiepileptic profile of the indirect pathway is exemplified following the attenuation of seizure activity after local administration of NMDA antagonists either in the SN or in the subthalamic nucleus. It would appear that both these pathways act through the SN control of seizure propagation, despite the fact that they exert opposite effects on SN neuronal activity.

As yet, it remains undetermined just how these pathways interact to control seizures or whether or not anatomical subpopulations of striatal efferents have the propensity to control specific types of seizure.

The prefrontal cortex is also served by dopaminergic neurones that have their soma located in the ventral tegmental area (VTA). Innervation of the prefrontal cortex from the VTA has been thought to be responsible for the modulation of cognitive processes in humans in addition to having a role to play in inhibiting spontaneous prefrontal neuronal firing. In the primate cortex, dopamine terminals have been shown to co-localize with glutamate terminals on dendritic spines of pyramidal neurones. Furthermore, dopaminergic terminals have been found to exist in close proximity to the dendrites of inhibitory interneurones. Thus, it appears that dopamine has the potential to provide a regulatory control over the degree of excitatory input into the cortex [118]. Indeed, dopamine has been shown to attenuate the spontaneous firing of rodent prefrontal neurones [119], possibly via an enhancement of the frequency and amplitude of spontaneous IPSCs [120].

Noradrenaline

Noradrenaline (NA) in the central nervous system is formed by the α-hydroxylation of dopamine and is considered to be primarily an inhibitory neurotransmitter. Attenuating synaptic NA levels has been shown to exert proconvulsant effects in models of seizure disorder [121], whereas increasing NA neurotransmission has been shown to reduce seizure activity [122]. Furthermore, synaptic noradrenergic activity has been shown to retard the kindling process (i.e. epileptogenesis) [115]. It has been proposed that the anticonvulsant activity of sodium valproate and carbamazepine can be partly attributed to their ability to heighten noradrenergic activity [123,124].

5-Hydroxytrytamine

5-Hydroxytrytamine (5HT) acts in the mammalian central nervous system through seven classes of receptor ($5HT_{1–7}$). At least four ($5HT_{1–4}$) are thought to modify neuronal excitability and/or neurotransmitter release [125].

In the brain, the prominent 5HT cell bodies are located in the raphe nuclei, which send ascending projections to the hippocampus [126]. 5HT has been shown to either inhibit or excite GABAergic interneurones in the CA1 region of the hippocampus following stimulation of $5HT_{1A}$ and/or $5HT_3$ receptors [127,128] and this has been proposed to modify excitatory responses within this region.

Serotonergic neurotransmission has been shown to influence the generation of certain types of seizure disorder in various experimental models, including hippocampal kindling [129] and systemic administration of proconvulsants [130]. One report comparing monoamines and their metabolites in brain tissue from epileptic patients undergoing temporal lobe resections for seizure control found that the compensatory activation of serotonergic neurotransmission that exists in human epilepsy generated an increase in 5HT turnover as reflected in cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA) levels. However, in this study, the increase in 5HT turnover rate was reported to be insufficient for blocking seizure activity [112]. Furthermore, pharmacological agents which enhance and facilitate 5HT neurotransmission have been shown to provide anticonvulsant effects in a wide range of experimental models of seizure disorder, including the genetically epilepsy-prone rat model of generalized tonic–clonic epilepsy (GEPR) [131]. Drugs such as the selective serotonin reuptake inhibitor (SSRI) fluoxetine have been shown to augment the synaptic concentration of 5HT and may be effective against generalized tonic seizures [132]. Antiepileptic drugs such as carbamazepine [116], sodium valproate [133] and zonisamide [134] have all been shown to elevate extracellular hippocampal 5HT levels in rodents. Lamotrigine has also been shown to elevate synaptic 5HT levels by inhibiting its uptake in synaptosomal preparations from rodent cortex [135].

Effects of antiepileptic drugs

Carbamazepine, phenytoin, valproate and zonisamide are four of the most commonly cited antiepileptic drugs associated with alterations in monoaminergic neurotransmission. All of these

antiepileptic drugs are thought to mediate their actions, at least in part, via a blockade of Na^+ channels [12,136–138]. It has been well established that blockade of Na^+ ion channels inhibits neuronal firing. However, at therapeutically relevant concentrations carbamazepine, phenytoin, valproate and zonisamide have been found to enhance monoamine neurotransmission [133,134,139]. Moreover, therapeutically relevant concentrations of carbamazepine and zonisamide have been shown to facilitate basal monoamine release without affecting basal glutamate release, and inhibited the depolarization-induced release of glutamate and monoamines [140]. This effect appears to be biphasic in that at supratherapeutic levels carbamazepine and zonisamide reduced brain monoamine concentrations [141,142]. The finding that carbamazepine produced a concentration-dependent increase in [^{3}H]5HT overspill without affecting Ca^{2+}- [116] or K^+-evoked neurotransmission [143] suggests that carbamazepine-induced 5HT release is not dependent on depolarization or exocytosis.

It is interesting to note that co-administration of zonisamide with either phenytoin or valproate increased brain concentrations of dopamine and 5HT compared with treatment with zonisamide alone [144]. It has previously been shown that zonisamide does not affect the pharmacokinetic properties of valproate [145] and therefore it would be interesting to discover whether polypharmacy involving zonisamide as add-on therapy to existing valproate treatment would yield greater clinical benefit than that seen with valproate monotherapy.

Intracellular signalling pathways

There are numerous intracellular signalling pathways that can be activated or inactivated by activity at membrane receptors (in particular metabotropic receptors described above) and, conversely, can modulate membrane receptors and channels. Such intracellular pathways may provide a powerful means of altering cellular excitability. Identifying the relevance of intracellular drug targets is, however, complex because of the intricate relationships between different intracellular processes and the consequent difficulty in distinguishing direct from indirect effects. Many of the effects on intracellular mechanisms may be important for the action of antiepileptic drugs in other conditions, especially psychiatric disorders, and as neuroprotectants [146]. Perhaps the antiepileptic drug that has been most studied in regards to intracellular targets because of its powerful mood-stabilizing effect is valproate. Valproate has been reported to inhibit histone deacetylase (HDAC) enzymes [147], which would increase gene expression and may contribute to an antitumour effect; inhibit glycogen synthase kinase-3 [148], perhaps contributing to its mood-stabilizing effect; modulate MAPK/ERK signalling [149], perhaps contributing to its neuroprotective effects; and attenuate inositol (1,4,5)-triphosphate (IP3) signalling [150], perhaps contributing to its effects in bipolar mood disorder. Carbamazepine shares some of these intracellular effects [146].

A potentially important intracellular target is the intraneuronal calcium store, which substantially contributes to the regulation of neuronal excitability, neurotransmission and regulation of gene expression and disease-related processes such as epileptogenesis [151,152]. Ca^{2+} release from these stores is mainly regulated by IP3 and ryanodine receptors. Some AEDs, such as levetiracetam [153], topiramate [154], zonisamide [155] and carbamazepine [156], were reported to modulate IP3 and ryanodine receptors. The extent to which these intracellular effects contribute to these drugs' efficacy in epilepsy is unclear. It has, for example, been postulated that many of the effects of topiramate on channels and receptors are mediated through an action of topiramate in inhibiting protein phosphorylation [157].

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8 Mechanisms of Tolerance and Drug Resistance

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Introduction

The primary aim of epilepsy therapy by antiepileptic drugs (AEDs) is seizure freedom. However, about one-third of patients with epilepsy have drug-resistant epilepsy. This is associated with an increased risk of death and debilitating psychosocial consequences and thus is one of the major problems in epilepsy therapy [1]. Drug-resistant epilepsy is defined as the persistence of seizures despite treatment with a range of AEDs, using different mechanisms of action singly or in combination at maximum tolerated doses. To overcome this problem, there is a pressing need to develop more effective treatments and strategies. To attain this goal, we need to understand the mechanisms underlying drug resistance. In this chapter, several possible mechanisms of drug resistance will be reviewed (Fig. 8.1). These mechanisms will be assigned to three major categories: (1) disease-related mechanisms; (2) drug-related mechanisms; and (3) pharmacogenetic mechanisms. As will be discussed in this chapter, development of tolerance, i.e. the reduction in response to an AED after repeated administrations, also constitutes an important drug-related mechanism of resistance, and is reviewed in the section on drug-related mechanisms of drug resistance in epilepsy.

Disease-related mechanisms of drug resistance in epilepsy

In this section we will examine the clinical evidence for hypotheses concerning disease-related mechanisms of drug resistance, which are both plausible and based on a reasonable body of evidence (Fig. 8.1). These are:

- epilepsy syndromes including their aetiology;
- progression of disease;
- structural brain alterations and/or network changes as assessed by studies of patients undergoing epilepsy surgery and, if possible, appropriate controls;
- alterations in drug targets; and
- alterations in drug uptake into the brain.

For our discussion it is worthwhile to note that several mechanisms outlined above may act together and possibly even interact. It is probably naïve to think that only one mechanism explains drug resistance in an individual patient. In addition, assessing the clinical evidence for disease mechanisms of drug resistance is fraught with a number of difficulties. There is no universal definition of drug resistance. Many authors define drug resistance as the persistence of seizures despite treatment with a range of AEDs used alone or in combination at maximum tolerated doses [1,2]. However, drug resistance is a graded process, and past treatment history has an effect on response. Although relative drug resistance can be identified after failure of two past drugs (see ref. 3), a significant minority of patients (17%) is rendered seizure free by addition of newly administered AEDs even after failure of two to five past AEDs [4]. Furthermore, the definition of seizure outcome in patients undergoing surgical or non-surgical treatment for drug resistance is often author specific and is thus difficult to compare between studies [5]. There are many clinical reasons why patients may be resistant to AED therapy. An incorrect diagnosis can lead to ineffective treatment. For example, use of carbamazepine in a patient with absence seizures and generalized spike–wave activity can exacerbate seizures. Likewise, treating a patient with complex partial seizures with ethosuximide is unlikely to be efficacious. Certain AEDs, such as gabapentin, pregabalin, vigabatrin and lamotrigine, can exacerbate myoclonic seizures [1,6]. Diagnostic issues, poor choice of AEDs or insufficient doses leading to inadequate drug treatment and failure to become seizure free will not be discussed here [1,6]. We will also not discuss mechanisms of co-morbidity or mortality associated with drug resistance in this chapter. Here, the clinical and experimental evidence for putative disease-related mechanisms of drug resistance will be reviewed.

Epilepsy syndrome associated with drug resistance

The underlying epilepsy syndrome is a significant predictor for drug resistance [1,7–9]. Children with one of the epileptic encephalopathies are most likely to have drug-resistant epilepsy, and those with symptomatic partial epilepsies are more likely to be drug resistant than those with other syndromes including idiopathic partial or generalized, cryptogenic partial, and unclassified epilepsies [8]. Clinical features, such as the epilepsy syndrome or the aetiology, may reasonably predict if temporal lobe epilepsy (TLE) in children will turn out to be drug resistant [9].

However, in some epileptic syndromes, the proportion of patients with drug-resistant epilepsy varies considerably and the determinants of this variation are largely unknown [1].

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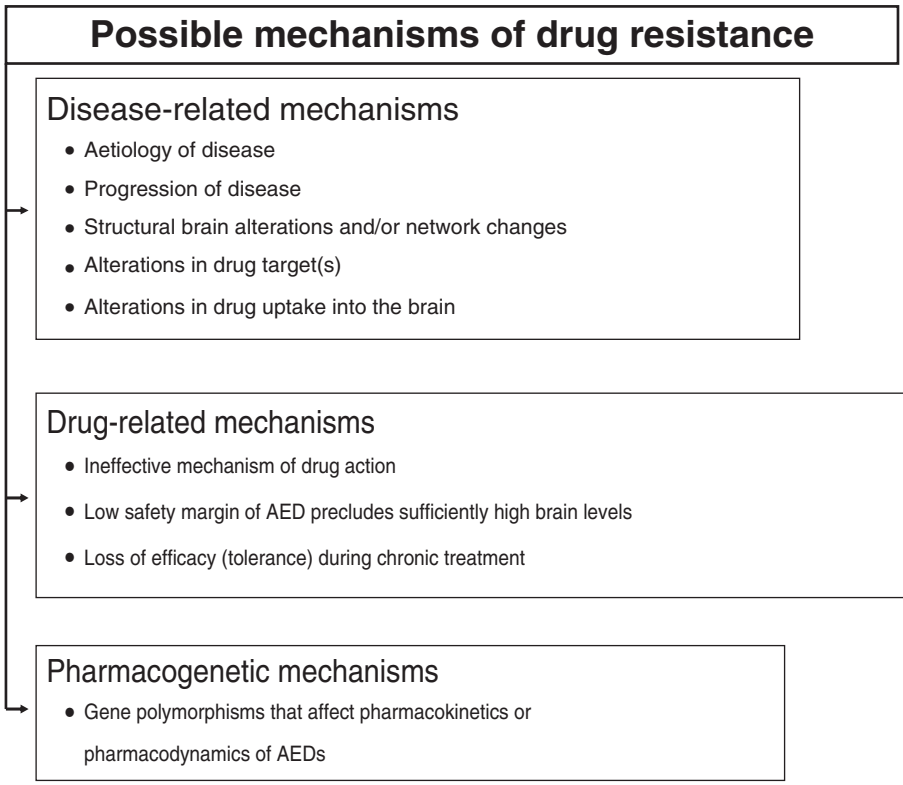

Fig. 8.1 Possible mechanisms of drug resistance. Adapted from ref. 57.

Progression of disease

Disease-related mechanisms of drug resistance may change in the course of the epilepsy. In a study of 613 children, around 70% were seizure free after 2 years, 20% were no longer seizure free having relapsed, and 10% had never been seizure free [8]. In a prospective, long-term population-based study of 144 patients followed for a median of 40 years since their first seizure before the age of 16 years, 19% of patients were drug resistant from the start to the end of follow-up, while a further 14% relapsed after remission and became drug resistant, indicating a worsening course of epilepsy [10]. On the other hand, 32% of patients became seizure free after a median of 9 years of treatment and remained seizure free to the end of follow-up. This longitudinal study provided incontrovertible evidence that the epilepsy may switch in a significant proportion of patients in the course of the disorder from being drug resistant to becoming controlled and vice versa [10]. In these patients, drug resistance and its underlying mechanisms have changed over time. Seizures themselves could, among other non-seizure-related factors, be involved in the generation of drug resistance. This hypothesis is supported by the observation that seizure clusters, defined as three or more seizures per 24 h, occurring often as many as 15 years after starting drug treatment, increased the risk of drug-resistant epilepsy by a factor of 3 compared with those without clusters [11]. In contrast, patients with seizure clustering prior to treatment versus no clustering showed no difference in seizure outcome [11].

Structural brain alterations and/or network changes

Resective surgery is standard care for eligible patients with drug-resistant epilepsy [12]. Long-term studies of clinical experience suggest that following temporal lobe surgery a median of 50–66% of patients with formerly drug-resistant TLE become seizure free with continued medical treatment, including 20–25% of patients who are seizure free without AEDs [14,15]. There is agreement that the best seizure outcome has been reported for patients with mesial TLE, particularly those with a structural lesion in the MRI [5]. Hippocampal sclerosis is a common finding in patients with pharmacoresistant TLE, so that it is often suggested that hippocampal sclerosis plays a causal role in the mechanisms underlying AED resistance [1]. However, as pointed out in a recent critical review on TLE surgery [16], it is quite difficult to be certain which specific structures of the medial temporal lobe need to be resected to eliminate drug resistance and allow a patient to become seizure free. In fact, a review of 53 studies addressing extent of resection in surgery for patients with TLE identified only seven prospective studies, of which four were randomized [16]. Schramm [16] noted that class I evidence concerning seizure outcome related to type and extent of resection of mesial temporal lobe structures is rare. Most studies reviewed found no positive correlation between extent of mesial resection and seizure freedom after surgery; even leaving hippocampus and amygdala untouched can result in seizure freedom rates of around 50% [16].

Another important issue that makes it difficult to determine which structures of the mesial temporal lobe are involved in generating or maintaining drug resistance is that the results of seizure freedom after surgery can be fully attributed to surgery only if no previously drug-resistant patients become seizure free without surgery [15,17]. However, apart from one 12-month randomized trial, the long-term seizure outcome of surgery versus medical treatment in non-operated patients is not well known [5,17,18]. In a study from Bonn, Germany, the seizure outcome of drug-resistant epilepsy, mostly TLE, was compared in patients undergoing surgery and in those who were ineligible for surgery. Both groups received medical treatment. Although 52% of surgical patients were seizure free in the last year of follow-up, as many as 24% of patients became seizure free without undergoing surgery, just with a change of medical regimen [19]. In addition, a number of clinical observations have reported that around 20% of formerly drug-resistant patients with partial epilepsy, including patients ineligible for surgery, become seizure free without surgery only through a change of medical regimen [20–22].

For the search for structural brain alterations associated with drug resistance, these findings have important implications. If AEDs are required to become seizure free, it is not unreasonable to consider that the effect of AEDs outside of the resected area is needed for seizure control after surgery. There is preliminary evidence from functional imaging [23,24] and from transcranial magnetic stimulation for changes in the contralateral hemisphere after successful temporal lobe surgery [25]. Extended changes in excitability and in functional imaging after surgery may be related to widespread functional impairment in patients with partial epilepsy and support the existence of network changes beyond the resected area in patients undergoing temporal lobe surgery. In addition, as noted above, only about half of all seizure-free surgical patients are seizure free when off AEDs. For the other half, it is not unreasonable to consider that AEDs are needed to target areas outside of the resected zone [17]. The network hypothesis of drug resistance after surgery is based on the existence of non-resected limbic or extralimbic seizure generators left behind during surgery. If AEDs protect from effects of non-resected limbic or extralimbic seizure generators, the surgical patient is seizure free on AEDs; if not, surgery has failed to suppress drug resistance. It is not unreasonable to consider that for patients whose limbic seizure generators have been completely removed or affected and who have no other active seizure generators, surgery will achieve seizure freedom when also off AEDs, as in 20–25% of patients undergoing temporal lobe surgery [17].

A further issue is that, in many (but not all [26]) studies, surgical outcome worsens over the years [13,17]. In a series of patients who were initially seizure free after temporal lobe surgery, the proportion that remained seizure free dropped from 76 out of 88 patients (86%) at 3 months after surgery to 9 out of 12 patients (75%) available for review after 9 years or 9 of 88 (10%) of all patients initially seizure free [27]. In a study of surgical patients with mostly TLE, who had been seizure free (allowing for simple partial seizures) 5 years after surgery, the proportion of seizure-free patients dropped from 100% at 5 years to approximately 50% at 15 years after surgery [28]. AED discontinuation in seizure-free patients has been shown to lead to relapse in one in three patients [29]. Although many other causes for early and late relapses exist that may be unrelated to the mechanism of drug resistance, this finding, if confirmed, also has implications for the search for a structure-related mechanism of drug resistance in TLE. If, in fact, patients who were seizure free after surgery return to having seizures despite AED treatment and thus become again drug resistant, mechanisms involving remodelling of brain circuitry outside of the resected area may be involved. This has been called in experimental models of epilepsy ‘rewiring the brain’ [30].

How can hippocampal sclerosis contribute to drug resistance? In the hippocampal formation, the dentate gyrus normally functions as a high-resistance gate or filter, preventing the propagation of synchronized activity from the entorhinal cortex into the seizure-prone hippocampus [31]. In patients with TLE and in animal models of TLE, this filter or ‘gatekeeper’ attribute of the dentate gyrus is compromised in that dentate granule cells form an interconnected synaptic network associated with loss of (GABA-ergic) hilar interneurones [31]. Indeed, loss of neurones in the hilus of the dentate gyrus, which is closely associated with development of granule cell disinhibition and hyperexcitability, has been proposed to be the common pathological denominator and primary network defect underlying development of a hippocampal seizure focus [31,32].

To address directly whether structural changes are causally related to AED resistance, we recently compared hippocampal damage in epileptic rats that either responded or did not respond to AED treatment [33,34]. In this model, spontaneous recurrent seizures develop after a status epilepticus induced by prolonged electrical stimulation of the basolateral amygdala. The response to prolonged daily administration of phenobarbital at maximum tolerable doses in epileptic rats of this model can be divided into two categories: a responder subgroup with control of seizures and a non-responder subgroup without any significant reduction in seizure frequency. The resistance to phenobarbital extends to other AEDs, including phenytoin, thus resembling the multidrug type of AED resistance in patients with intractable TLE. This model thus offers unique approaches to the biological basis of refractoriness, particularly because pathological alterations in such AED-resistant rats can be directly compared with those of rats that do respond to AEDs. In most (>90%) non-responders of this model, we determined a significant loss of neurones in the CA1, CA3c/CA4 and dentate hilus, whereas most (>90%) of the responders did not differ in hippocampal morphology from non-epileptic controls, resulting in a highly significant difference between pharmacoresistant and responsive epileptic rats [33,34]. Based on these observations, it appears that the functional alterations in the dentate gyrus developing as a response to hilar cell loss are critically involved in the mechanisms underlying the refractoriness of seizures to AED treatment. Such structural and functional network changes will also affect AED targets, as will be discussed in the next section.

Alterations in drug targets

The target hypothesis of AED resistance in epilepsy suggests that acquired alterations to the structure and/or functionality of target ion channels and neurotransmitter receptors underlie drug resistance [35]. To exhibit antiepileptic activity, a drug must act on one or more target molecules in the brain. These targets include

voltage-dependent ion channels, neurotransmitter receptors and transporters or metabolic enzymes involved in the release, uptake and metabolism of neurotransmitters [36]. The target hypothesis is primarily based on studies with carbamazepine on voltage-gated sodium channels in hippocampal neurones. Voltage-gated Na^+ channels are ubiquitously expressed in excitable cells and appear to be targets for multiple first-line AEDs, including carbamazepine, phenytoin and lamotrigine.

To our knowledge, Wytse Wadman's group [37] was the first to report a loss of carbamazepine's modulatory effects on sodium channels in hippocampal neurones of patients with intractable epilepsy. The group found that the modulation of sodium current inactivation by carbamazepine in hippocampal CA1 neurones from patients with TLE and mesial temporal sclerosis was only half of that encountered in neocortical neurones from the same patients, and only half of that encountered in CA1 neurones from patients without mesial temporal sclerosis [37]. More recently, Heinz Beck's group [38] substantiated and extended these data by showing that the use-dependent block of voltage-dependent Na^+ channels of dentate granule cells by carbamazepine is completely lost in patients with carbamazepine-resistant TLE in comparison with patients clinically responsive to this AED. In addition to the loss of use-dependent inhibition of Na^+ channels by carbamazepine, the fast recovery from inactivation of the fast Na^+ current was carbamazepine insensitive in pharmacoresistant patients, whereas recovery was markedly slowed in cells from carbamazepine-responsive patients [38]. Consistent with these data from patients with intractable TLE, Remy *et al*. [38] also showed that use-dependent block of Na^+ channels by carbamazepine in dentate granule cells is absent in the pilocarpine rat model of TLE. Based on these data, the authors suggested that a loss of Na^+ channel drug sensitivity may explain the development of drug-resistant epilepsy. In a subsequent study in the rat pilocarpine model in TLE, Remy *et al*. [39] demonstrated that the effects of phenytoin on fast recovery from inactivation of Na^+ channels of hippocampal granule neurones were significantly reduced, though not to the same degree as observed with carbamazepine, substantiating the concept that reduced pharmacosensitivity of Na^+ channels may contribute to the development of drug resistance. In contrast to carbamazepine and phenytoin, lamotrigine slowed the time-course of recovery from fast inactivation in both epileptic and control rats without significant inter-group difference [39]. In the pilocarpine model, a loss of sensitivity of sodium channels to carbamazepine and phenytoin was also found in hippocampal CA1 neurones, although the loss of AED sensitivity was less pronounced in CA1 neurones than in dentate granule neurones [40]. Thus, the results of Beck and colleagues suggested that target mechanisms of drug resistance are cell type and AED specific.

Which mechanisms can account for altered sensitivity of Na^+ channels in CA1 or dentate granule cells in epileptic tissue? One possibility is that the subunit composition of these channels is altered, resulting in channels with lower AED sensitivity [35]. Several changes in Na^+ subunit expression have been observed in both human and experimental epilepsy [35]. For instance, in the pilocarpine model of TLE, the accessory β_1- and β_2-subunits were down-regulated, which was suggested to play a role in the altered pharmacosensitivity of Na^+ channels [41]. This view is supported by a study by Lucas *et al*. [42] showing that a mutation in the β_1-subunit of the voltage-gated sodium channel results in a dramatic loss of channel sensitivity to phenytoin.

A critical question in studying target alterations in epilepsy is the relation of changes at the cellular level to AED sensitivity *in vivo*. While such a correlation has been observed in patients with TLE [38,43], such a correlative analysis has not yet been performed for the pilocarpine model of TLE, which has been used in most studies by Beck's group. We used the kindling model of TLE to study whether AED responders and non-responders differ in pharmacological sensitivity of voltage-dependent sodium channels [44]. Responders and non-responders were selected by repeated testing with phenytoin *in vivo*, followed by evaluation of phenytoin's *in vitro* effects on voltage-gated Na^+ channels of hippocampal CA1 neurones. The *in vivo* resistance to phenytoin was not associated with altered tonic block of Na^+ channels by phenytoin, but recovery from Na^+ channel inactivation and use-dependent blocking effects were not analysed in this study [44].

Apart from voltage-dependent Na^+ channels, other drug targets, such as GABA-mediated inhibition, may be altered in patients with intractable epilepsy. Using the rat pilocarpine model of TLE, Brooks-Kayal *et al*. [45] demonstrated that expression of $GABA_A$ receptor subunit mRNAs is substantially altered in hippocampal dentate granule cells of pilocarpine-treated rats compared with controls. These changes in $GABA_A$ receptor subunit expression correlated with profound alterations in receptor function and pharmacology [45–47]. In normal granule cells, $GABA_A$ receptors of dentate granule cells are insensitive to zinc, which is released from mossy fibres and functions as a negative allosteric modulator of $GABA_A$ receptors. This zinc insensitivity of normal $GABA_A$ receptors is a result of high levels of expression of the α_1-subunit in these cells [46]. In epileptic rats, expression of the α_1- and β_1-subunits decreases and expression of α_4- and δ-subunits increases, leading to an assembly of $GABA_A$ receptors that are strikingly zinc sensitive. In addition to the enhanced zinc sensitivity, $GABA_A$ receptors from the epileptic hippocampus lose their sensitivity to augmentation by the benzodiazepine type site I modulator, zolpidem [48]. Coulter [46,47] has proposed that this temporal and spatial juxtaposition of these pathophysiological alterations may compromise the normal 'gatekeeper' function of the dentate gyrus through dynamic zinc-induced failure of inhibition, predisposing the hippocampal circuit to generate seizures. Of course, assuming that similar alterations in $GABA_A$ receptor function and pharmacology also take place in the epileptogenic human hippocampus, this could lead to reduced efficacy of AEDs acting via GABA-mediated inhibition.

We have recently examined whether AED-resistant rats differ from AED responders in expression and pharmacological sensitivity of $GABA_A$ receptors [33,34]. Phenobarbital-resistant rats differed strikingly from responsive rats in autoradiographic imaging of diazepam-sensitive and -insensitive $GABA_A$ receptor binding in the dentate gyrus with a significant shift to enhanced diazepam-insensitive binding in non-responders [33]. To address the hypothesis that diazepam-insensitive receptors contain the α_4- and δ-subunits that mediate tonic inhibition in the dentate gyrus, the expression of various $GABA_A$ receptor subunits was determined in AED responders and non-responders [34]. In non-

responders, decreased expression of various subunits, including α_1, $\beta_{2/3}$ and γ_2, was observed in CA1, CA2, CA3, and dentate gyrus, whereas much less widespread alterations were determined in responders. Furthermore, up-regulation of the α_4-subunit was observed in CA1 pyramidal cells of non-responders. Phenobarbital's anticonvulsant effect is thought to be primarily related to enhancement of GABA-mediated inhibitory synaptic transmission via modulation of $GABA_A$ receptors [36]. Although the effects of barbiturates on the $GABA_A$ receptor depend largely on the β-subunit, their agonist activity is substantially influenced by the α-subunit subtype. The marked decreases in β- and α-subunits observed in phenobarbital non-responders are likely to reduce the effect of phenobarbital on $GABA_A$ receptors and thus could be involved in the lack of anticonvulsant efficacy of phenobarbital in these animals. Profound alterations in $GABA_A$ receptor subtype expression have also been reported in patients with AED-resistant TLE [49]. The concomitant alterations in $GABA_A$ receptor expression and hippocampal morphology in pharmacoresistant rats of our model of TLE suggest that structural and functional network changes will also affect AED targets [33,34]. A similar association between structural changes and $GABA_A$ receptor expression has also been reported in patients with AED-resistant TLE [49].

Further evidence that changes in $GABA_A$ receptors occur during epileptogenesis that can lead to drug resistance comes from a series of studies of Bob Macdonald's and Claude Wasterlain's groups using the pilocarpine model [50,51]. These groups demonstrated that during a pilocarpine-induced status epilepticus there is a substantial reduction of potency for termination of seizures by AEDs that enhance $GABA_A$-mediated inhibition, such as benzodiazepines and phenobarbital. This progressive development of pharmacoresistance during a sustained status epilepticus is paralleled by alterations in the functional properties of dentate granule cell $GABA_A$ receptors. It was concluded that rapid modulation of $GABA_A$ receptors during status epilepticus may result in pharmacoresistance to AEDs that enhance $GABA_A$ receptor-mediated inhibition [50]. More recently, Goodkin *et al.* [52] and Naylor *et al.* [53] showed that internalization of $GABA_A$ receptors, i.e. trafficking of these receptors from the synaptic membrane to submembranous compartments, causes a decrease in the number of functional postsynaptic $GABA_A$ receptors that is likely to explain the pharmacoresistance to GABA-mimetic AEDs in status epilepticus.

Other than alterations in $GABA_A$ receptor subunit expression and receptor trafficking, there is a third potential mechanism to explain loss of pharmacological sensitivity of these receptors: a shift from adult inhibitory to neonatal excitatory $GABA_A$ receptors [54]. Such a shift in GABAergic response polarity from hyperpolarizing to depolarizing has been described in human epileptic neurones recorded in the subiculum of hippocampal slices obtained from resections in patients suffering from mesial TLE [55]. This shift is thought to be a result of increased intraneuronal Cl^- levels, caused by increased neuronal expression of NKCC1, an inwardly directed Na^+–K^+–$2Cl^-$ cotransporter that facilitates the accumulation of intracellular Cl^-, and down-regulation of KCC2, an outwardly directed K^+–Cl^- cotransporter [56]. Up-regulation of NKCC1 and down-regulation of KCC2 in the hippocampus have been described both in patients with TLE and in the kindling model of TLE. We currently plan to examine whether the brain expression of these chloride transporters differs in phenobarbital-responsive and -resistant epileptic rats.

As a proof-of-principle for the target hypothesis, it will be important to demonstrate that AED-resistant subgroups of patients differ from AED-responsive subgroups in their AED target sensitivity. Such a proof-of-principle is difficult to obtain in patients, because, in contrast to patients with intractable epilepsy, patients responding to AEDs in general do not undergo surgical treatment for their epilepsy. Although Remy *et al.* [38] obtained surgical 'reference' specimens from two patients who responded well to treatment with carbamazepine for comparison with 10 patients with carbamazepine-resistant TLE, differences in age, gender, history of epilepsy and AED treatment and various other variables may form a bias for such a comparison. As illustrated by our recent studies, animal models of TLE allowing selection of age-matched AED responders and non-responders may be useful to further evaluate the target hypothesis. Although the target hypothesis is a novel and biologically plausible theory to explain drug resistance, the fact that most patients resistant to AED treatment are resistant to a broad range of AEDs with different mechanisms of action suggests that other less mechanism-specific factors contribute to drug resistance. The most prominent hypothesis in this respect, the transporter hypothesis, which was first explored in chemotherapy-resistant cancer, currently attracts growing interest as one further putative mechanism to explain drug resistance in epilepsy by reduced penetration of AEDs into the brain.

Multidrug transporter hypothesis

The importance of (multi)drug efflux transporters, such as P-glycoprotein (P-gp), in disease processes and treatment has become increasingly evident in recent years [57,58]. Drug efflux transporters have a major impact on the pharmacological behaviour of most clinically used drugs, critically affecting drug absorption, disposition, and elimination in the body [59]. Furthermore, such transporters are involved in the emergence of multidrug resistance (MDR), which plays an important role in the failure of treatments of tumours, infectious diseases and several brain disorders, including epilepsy [57,58,60]. P-gp, the encoded product of the human multidrug resistance-1 (*MDR1*; *ABCB1*) gene, is of particular clinical relevance in that this transporter has a broad substrate specificity (which led to the term multidrug transporter), including a variety of structurally divergent drugs in clinical use today [61]. Furthermore, P-gp is expressed by tissues with excretory function (small intestine, liver and kidney) and at blood–tissue barriers [blood–brain barrier (BBB), blood–testis barrier and placenta], thus limiting drug entry into the body after oral administration, promoting drug elimination into bile and urine, and limiting drug penetration into sensitive tissues such as the brain [61].

In the BBB, multidrug transporters such as P-gp, members of the multidrug resistance protein (MRP) family and breast cancer-related protein (BCRP) are located in brain capillary endothelial cells that form the BBB and combine to reduce the brain penetration of many drugs [57,58]. This phenomenon of multidrug resistance is a major hurdle when it comes to the delivery of therapeutics to the brain. Therefore, the development of strategies for bypassing the influence of these drug efflux transporters,

for the design of effective drugs that are not substrates, and for the development of inhibitors for the transporters has become an imperative for the pharmaceutical industry [62].

Tishler *et al*. [63] were the first to report that brain expression of *MDR1*, which encodes P-gp in humans, is markedly increased in the majority of patients with medically intractable partial (mostly temporal lobe) epilepsy. Based on their findings, Tishler *et al*. [63] proposed that P-gp may play a clinically significant role by limiting access of AEDs to the brain parenchyma, so that increased P-gp expression may contribute to the refractoriness of seizures in patients with treatment-resistant epilepsy. Following the report by Tishler *et al*. in 1995 [63], the finding of *MDR1*/P-gp overexpression in epileptogenic brain tissue of patients with drug-refractory epilepsy was confirmed by several other groups [1,57,58,64]. Furthermore, it was shown that, in addition to P-gp, several MRPs, but not BCRP, are overexpressed in brain capillary endothelial cells and/or astrocytes of pharmacoresistant patients [1,58,65]. In some of these studies, the overexpression of drug efflux transporters in astrocytes appeared most marked around blood vessels. In view of data indicating that the endothelial barrier function of the BBB is transiently disrupted during seizures [65], overexpression of multidrug transporters in astroglial endfeet covering the blood vessels may represent a 'second barrier' under these conditions. As a consequence, overexpressed multidrug transporters may lower the extracellular concentration of AEDs in the vicinity of the epileptogenic pathology and thereby render the epilepsy caused by these pathologies resistant to AED treatment.

An open question is whether the overexpression of P-gp and MRPs in epileptogenic brain tissue of patients with intractable epilepsy is intrinsic (constitutive) or acquired, i.e. a consequence of epilepsy, of uncontrolled seizures, of chronic treatment with AEDs, or of combinations of these factors. Because treatment-resistant patients have no fewer neurotoxic side-effects under AED treatment than patients who are controlled by AEDs, the overexpression of drug transporters in treatment-resistant patients is most likely restricted to the epileptic focus or circuit. This is substantiated by a previous study of Sisodiya *et al*. [66] in which overexpression of P-gp and MRP1 was found in epileptogenic tissue but not in adjacent normal tissue of the same patients.

In animal models of TLE, such as the kindling and kainate models, a transient overexpression of P-gp was found in brain capillary endothelial cells, astroglia and neurones following seizures [1,58], indicating that seizures themselves can induce overexpression of drug transporters. This could explain why one of the major predictors of drug resistance is high seizure frequency (or density) prior to initiation of treatment [7]. However, constitutive rather than induced or acquired overexpression of multidrug transporters has been reported in patients with malformations of cortical development [67]. In addition to intrinsic or acquired overexpression of multidrug transporters in the BBB of patients with epilepsy, polymorphisms in transporter genes may play a role in drug resistance (see below). Furthermore, alterations in expression and functionality of multidrug transporters in patients with intractable epilepsy need not necessarily be restricted to the brain but could also occur in other tissues, such as the small intestine, where P-gp is thought to form a barrier against entrance of drugs from the intestinal lumen into the bloodstream, thereby limiting their oral bioavailability [61]. In this respect, it is interesting to note that Lazarowski *et al*. [68] have reported persistent subtherapeutic plasma levels of AEDs (including phenytoin and phenobarbital) despite aggressive and continuous AED administration in patients with refractory epilepsy that was associated with overexpression of *MDR1*.

In view of the emerging evidence that multidrug transporters are overexpressed in epileptogenic brain tissue, particularly in capillary endothelial cells and astrocytes, contributing to BBB permeability, it is important obviously to know whether AEDs are substrates for these transporters. The first indication that AEDs are substrates for P-gp came from experiments by Tishler *et al*. [63], who found that intracellular phenytoin levels in an *MDR1*-expressing neuroectodermal cell line were only one-quarter of that in *MDR1*-negative cells, suggesting that P-gp significantly contributes to cell export of phenytoin. Phenytoin transport by P-gp was also demonstrated in a kidney epithelial cell line transfected with the rodent *mdr1a* cDNA, which could be blocked by the P-gp inhibitor PSC833 [69].

More recently, Rizzi *et al*. [70] demonstrated that *mdr1a/b* knockout mice, which lack P-gp, exhibit a significant 50% increase in phenytoin levels in the hippocampus compared with wild-type mice. *Mdr1* knockout mice were also used to demonstrate P-gp transport of carbamazepine [70] and topiramate [71]. By using a rat microdialysis model with microdialysis probes in both brain hemispheres and local (cerebral) inhibition of multidrug transporters in one hemisphere, we have previously demonstrated that several major AEDs are substrates for either P-gp or MRPs, or both [58]. In general, the data from these different experimental approaches indicate that several major AEDs (phenytoin, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, felbamate, topiramate) are substrates for P-gp and some of them (phenytoin, valproate) seem also to be transported by MRPs at the BBB [58].

However, the situation is not straightforward. Recent data from our group demonstrated species differences in the transport of AEDs by P-gp in that significant transport could be demonstrated with rodent but not human P-gp in an *in vitro* transport assay [72]. In this respect, it is important to note that most AEDs are highly lipophilic, a property which could conceal asymmetrical transport in *in vitro* transport assays that are commonly used for identifying P-gp substrates. This prompted us to modify such assays in a way that allows evaluation of active transport independently of the passive permeability component, demonstrating transport of several major AEDs, including phenytoin, phenobarbital and lamotrigine, by human P-gp [73]. Using an *in vitro* BBB model with human capillary endothelial cells from either normal brain or drug-resistant epileptic brain, Cucullo *et al*. [74] recently reported a dramatically reduced permeability of phenytoin across the *in vitro* BBB formed from endothelial cells of patients with refractory epilepsy, which could be partially counteracted by the selective P-gp inhibitor tariquidar, substantiating transport of AEDs by human P-gp.

In view of the overexpressed efflux transporters found in epileptogenic brain tissue of patients with pharmacoresistant epilepsy and animal models of epilepsy, another important question is whether this overexpression lowers brain uptake of AEDs. By

using the kainate model of TLE in mice, Rizzi *et al*. [70] demonstrated that the significant increase in *mdr1* mRNA expression measured by reverse transcriptase polymerase chain reaction (RT-PCR) in the hippocampus after kainate-induced seizures was associated with a 30% decrease in the brain–plasma ratio of phenytoin, thus substantiating the view that P-gp alterations significantly affect concentrations of AEDs in the brain. More recently, van Vliet *et al*. [75] reported decreased brain levels of phenytoin that were restricted to brain regions with increased expression of P-gp in epileptic rats, which could be counteracted by inhibiting P-gp. In patients with oxcarbazepine (OXC)-resistant epilepsy, the brain tissue expression of *ABCB1* mRNA was found to be inversely correlated with brain levels of 10-OHCBZ (10,11-dihydro-10-hydroxy-5H-dibenzo(b,f)azepine-5-carboxamide), the active metabolite of OXC, indicating that P-gp may play a role in the pharmacoresistance to OXC by causing insufficient concentrations of its active metabolite at neuronal targets [76].

A further important step in the evaluation of the multidrug transporter hypothesis of drug-resistant epilepsy was the demonstration that rats that do not respond to AEDs exhibit significantly higher expression levels of P-gp in brain capillary endothelial cells of the BBB than AED-responsive rats [77,78]. This was demonstrated for two different rat models of TLE: phenytoin-resistant kindled rats and phenobarbital-resistant rats with spontaneous recurrent seizures [77,78].

If drug resistance is due to such processes, it should be possible to demonstrate that the inhibition or avoidance of the resistance-mediating mechanism counteracts drug resistance in epilepsy. Some indirect, correlative evidence came from experiments with diverse AEDs in pharmacoresistant kindled rats, selected by repeated testing with phenytoin [79]. As described above, these phenytoin-resistant rats have an increased expression of P-gp in focal epileptogenic brain tissue. All AEDs that were substrates for P-gp showed absent or low anticonvulsant efficacy in phenytoin non-responders [79,80]. The only exception was levetiracetam, which was equally efficacious in responders and non-responders [79] and seems not to be a substrate for rat P-gp [81]. A further important step is to examine whether P-gp inhibitors counteract multidrug resistance. For this purpose, we used epileptic rats that were either responsive or resistant to phenobarbital [82]. In resistant animals, coadministration of the selective P-gp inhibitor, tariquidar, together with phenobarbital reversed resistance, leading to seizure control in animals that were resistant to phenobarbital alone [82]. That such a strategy may be functioning in patients with epilepsy is suggested by a recent anecdotal report by Summers *et al*. [83] on a single patient with intractable epilepsy in whom the P-gp inhibitor verapamil was added to the AED regimen. A similar clinical improvement after verapamil was reported by Iannetti *et al*. [84]. However, such an anecdote is weak evidence. The effects of more selective P-gp inhibitors, such as tariquidar or elacridar, are currently unclear.

Drug-related mechanisms of drug resistance in epilepsy

Antiepileptic drugs themselves may contribute to drug resistance (Fig. 8.1). First, the mechanisms of action of available AEDs is an important consideration. AEDs with novel mechanisms of action can control seizures that other drugs have failed to control. Second, the risk–benefit ratio (safety margin) of AEDs, i.e. the ratio between adverse (or toxic) and antiepileptic effects, may prevent the achievement of sufficiently high AED levels to suppress a specific type of epilepsy or seizures. Thus, development of an AED with better tolerability may allow control of this type of epilepsy. Third, development of tolerance to the antiepileptic activity of an AED can result in resistance.

Development of tolerance, i.e. the reduction in response to a drug after repeated administrations, is an adaptive response of the body to prolonged exposure to the drug, and tolerance to AEDs is no exception (see ref. 85 for a detailed review of this topic). Tolerance develops to some drugs effects much more rapidly than to others. The extent of tolerance depends on the drug and individual genetic factors. Tolerance to adverse effects of AEDs is well known and clinically accepted, but there is increasing evidence that tolerance may also lead to loss of efficacy of AEDs and is reversible after discontinuation of drug treatment. There are two major types of tolerance: pharmacokinetic and pharmacodynamic. Pharmacokinetic (metabolic) tolerance is due to induction of AED-metabolizing enzymes, and has been shown for most first-generation AEDs, but is easy to overcome by increasing dosage. However, in addition to increasing their own metabolism, AEDs may affect their distribution into the brain by increasing the expression of P-gp; this is a new type of pharmacokinetic tolerance that may also affect newer AEDs [85]. The second type of tolerance is pharmacodynamic (functional) tolerance, which is due to 'adaptation' of AED targets, by loss of receptor sensitivity for example, and has been shown experimentally for all AEDs that lose activity during prolonged treatment [85]. Functional tolerance may lead to complete loss of AED activity and cross-tolerance to other AEDs. There is convincing experimental evidence that almost all first-, second- and third-generation AEDs lose their antiepileptic activity during prolonged treatment, although to a different extent [85]. Because of diverse confounding factors, detecting tolerance in patients with epilepsy is more difficult but can be done with careful assessment of decline during long-term individual patient response. After excluding confounding factors, tolerance to antiepileptic effect for most modern and old AEDs can be shown in small subgroups of responders by assessing individual or group response [85]. Development of tolerance to the antiepileptic activity of an AED is likely to be one important reason for failure of drug treatment.

Pharmacogenetic mechanisms of drug resistance in epilepsy

Drug treatment of epilepsy is characterized by unpredictability of efficacy, adverse drug reactions and optimal doses in individual patients, which, at least in part, is thought to be a consequence of genetic variation [86]. It is becoming increasingly clear that genetic variation plays an integral role in variability of both AED pharmacokinetics and pharmacodynamics. Single-nucleotide polymorphisms (SNPs), variations at a single site in the DNA, are the most frequent form of sequence variations in the human genome and can affect the efficacy, tolerability and duration of

action of AEDs. Drug targets and drug transporters can be affected by genetic variation. In terms of AED targets, so far the most interesting data have been accrued for voltage-dependent Na^+ channels [87]. In studies on genetic variation in *SCN1A*, the gene encoding for the α-subunit of the voltage-gated neuronal sodium channel, associations of functional SNPs with clinical response to phenytoin, carbamazepine, lamotrigine and oxcarbazepine were reported [87,88].

Polymorphisms in various candidate drug transporter genes have been evaluated, including variation in the *MDR1* (*ABCB1*) gene, which encodes P-gp, to determine whether these are associated with variation in AED response in patients with epilepsy [86]. A common SNP (C3435T) identified within exon 26 of the *MDR1* gene has been reported to be associated with differential expression and function of P-gp [89]. Siddiqui *et al*. [90] were the first to report that patients with multidrug-resistant epilepsy were significantly more likely to be homozygous for the C allele than the T allele; however, this was not confirmed by several subsequent studies [86]. One major reason for inconsistent data on this polymorphism may be that several of the associated genetics studies involved AEDs that are not transported by human P-gp. Two recent studies on patients undergoing monotherapy with AEDs (phenytoin or phenobarbital) that are transported by human P-gp showed that pharmacoresistance was much more frequent in patients with the CC genotype of the *MDR1* C3435T polymorphism [91,92]. Furthermore, the study by Basic *et al*. [92] indicated that the CC genotype is associated with lower cerebrospinal fluid levels of phenobarbital than the CT or TT genotype. However, causality has not been proven in any of these studies, but all reported findings remain interesting associations. Future ongoing studies with specific P-gp inhibitors may be able to extend the evidence from association to causation.

Conclusions

Although AEDs are very useful in blocking seizures, many patients do not respond adequately to these agents. In order to enhance our understanding about the mechanisms of pharmacoresistance in epilepsy and thereby develop new strategies for more efficacious treatments, studies on brain tissue from drug-resistant patients and suitable experimental models of intractable epilepsy are mandatory. There is increasing evidence from studies on epileptic brain tissue that AED target alterations and overexpression of multidrug transporters may be important mechanisms of pharmacoresistance, and both mechanisms of refractoriness may coexist in the same epileptogenic brain tissue. Target and transporter alterations in patients with epilepsy may be a consequence of the disease, the treatment, genetic factors or combinations of these possibilities. In addition, structural brain alterations in focal epileptogenic tissue, for example hippocampal sclerosis or cortical dysplasia, and beyond may be involved in rendering epilepsy drug resistant. Furthermore, long-term, progressive changes in neural networks during development and progression of epilepsy may lead to reduced pharmacosensitivity. However, much of the evidence is correlative in nature. As outlined in this chapter, there are several other potential mechanisms contributing to pharmacoresistance (including tolerance) that have to be dealt with when thinking about effective therapeutic agents for hitherto intractable types of epilepsy. Thus, development of novel pharmacological and surgical strategies for improved treatment of drug-refractory epilepsy is now, and will be in the future, a complex venture.

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2

Section 2
Principles of Medical Management

The Treatment of Epilepsy, Third Edition Edited by S. Shorvon, E. Perucca and J. Engel
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9 General Principles of Medical Management

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The medical management of epilepsy requires more than knowledge of the clinical pharmacology of antiepileptic drugs. In fact, many factors need to be considered for rational management decisions. To start with, determining whether treatment is indicated requires assessment of the risk–benefit ratio in the individual patient, which, in turn, is influenced not only by the type and the frequency of the seizures, but also by age, gender, associated medical conditions and the impact of potential adverse effects of available treatment options on the patient's quality of life. A thorough diagnostic evaluation is essential in this process because the type of treatment, its duration and long-term prognosis are dependent upon a correct identification of seizure types and, whenever possible, of the underlying epilepsy syndrome and related aetiological factors.

Although achieving seizure control is a most important objective, seizures are not the only cause for concern in patients with epilepsy. Any associated neurological, psychological, psychiatric and social handicaps need to be equally addressed. Patients and their caregivers need to be informed about the nature of the disease, its prognostic implications, the objectives of therapy, the risks and benefits of drug treatment (including the risks associated with poor compliance and with abrupt drug withdrawal) and the availability of alternative therapeutic strategies, including epilepsy surgery. Medical management should also involve a discussion of factors that could impact negatively on seizure control, without placing undue restrictions on the patient's lifestyle. Counselling about marriage, reproduction, driving regulations and other legal matters may be indicated. Even in affluent societies, epilepsy is still associated with stigma, and affected patients may suffer more from prejudice and discrimination than from the actual manifestations of the disease. As a result, psychological and social support is often required and represents a major component of clinical management in individual cases.

The purpose of this chapter is to review the general principles of medical management. Specific therapeutic strategies in relation to the stage of the disease and to individual characteristics, including age, gender, associated learning disability, other comorbidities and associated drug treatments, are discussed in detail in the following chapters, while the criteria for choosing specific antiepileptic drugs are addressed in Chapter 30.

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Aims of treatment

The primary goal of treatment is to ensure the best possible quality of life that is compatible with the nature of the patient's seizure disorder and with any associated mental or physical disabilities [1,2]. To achieve this general goal, various objectives need to be addressed whenever relevant or feasible.

Complete seizure control

If exception is made for the control of ongoing seizures and status epilepticus, the treatment of epilepsy is primarily prophylactic (e.g. aimed at preventing seizure recurrence). Prospective studies have demonstrated that there is a world of difference for some individuals' quality of life between a state of complete seizure freedom and even rare seizures separated by long intervals [3]. In general terms, therefore, the primary objective of treatment should be complete seizure control where this is feasible. This, however, should not be achieved at all costs. Antiepileptic drugs can produce severe adverse effects, particularly when they are administered at high dosages or in combination, and the situation should never arise where a patient is made to suffer more from the adverse effects of treatment than from the symptoms of the disease [4]. Whenever complete seizure freedom proves to be a non-realistic goal, optimal treatment should result from the best compromise between the desire to minimize seizure frequency and the need to maintain adverse effects within acceptable limits.

Reduction of seizure severity

Although most outcome studies in epilepsy have focused on seizure frequency, seizure severity, particularly with respect to occurrence of potentially injurious ictal manifestations, is by itself an important determinant of quality of life [5]. In patients whose seizures cannot be controlled completely, it makes sense to aim at suppressing preferentially those seizures which are most disabling. For example, in patients with Lennox–Gastaut syndrome, controlling drop attacks may produce greater benefit than suppressing associated partial or atypical absence seizures. Likewise, a treatment that will prevent secondary generalization would be expected to have a major impact on the quality of life of a patient with simple sensory partial seizures. Indeed, antiepileptic drugs may have differential effects on the components of ictal events and seizure spread, by suppressing or modifying the type or the duration of auras, convulsive manifestations, associated autonomic features and postictal events [6]. Assessing the most disabling seizure types can require assistance from an external

observer, but the patient's perceptions are more important. A seizure component that may appear trivial or negligible to an observer may be perceived as very distressing by the patient. Unfortunately, the ways in which antiepileptic drugs modify seizure components have been little studied, but in individual patients this aspect may have an important impact on management decisions.

Avoidance of adverse effects

The prescription of antiepileptic medication entails a significant risk of adverse effects. While many patients with recently diagnosed epilepsy can be controlled at low dosages, which produce only modest detectable toxicity [7], patients with severe epilepsies may have to pay a significant price in terms of adverse effects to avoid or minimize seizure recurrence.

It has been shown that, particularly in patients with refractory epilepsies, quality of life may be affected to a greater extent by the adverse effects of medication than by the occurrence of seizures [8]. This should be kept in mind to avoid overtreatment, and a strategy to reduce drug toxicity should be part of routine management (Chapter 22). There is evidence that physicians do not pay sufficient attention to the adverse effects of medications, and that use of simple self-administered questionnaires for the screening of adverse effects can do much to improve clinical outcome [8].

Occasionally, patients in whom available medications do not seem to have any significant effect on their seizures are encountered. These patients are only harmed by antiepileptic drugs, and physicians should be prepared to accept that the best management in such cases is not to prescribe any drug at all. Treatment may also not be indicated in patients with very infrequent seizures, especially when these occur only at night or in relation to predictable and avoidable precipitating events, such as severe sleep deprivation, or have no important impact on the patient's psychological, social or professional conditions.

Suppression of subclinical epileptic activity

Antiepileptic drug therapy should be aimed primarily at suppressing the clinical manifestations of seizures, and normalization of the electroencephalogram (EEG) generally is neither a major nor an attainable objective, nor in some cases even desirable. In certain situations, however, suppression of epileptiform EEG abnormalities is a justifiable therapeutic goal. This is the case when there is a close correlate between clinical seizures and EEG paroxysms, and the seizures are not easily quantifiable clinically, as in childhood absence epilepsy or some photosensitive epilepsies. The EEG may also be important in guiding treatment in infants and children with severe epileptiform EEG abnormalities co-existing with brain dysfunction: in these situations, the extent of EEG-related dysfunction should be determined, and vigorous treatment may be needed to abate its effects (see Chapters 13 and 14). In the syndrome of continuous spike–waves during sleep (CSWS), for example, the occurrence of electrical status epilepticus during sleep plays a key role in causing cognitive regression, and the intellectual development of these children improves dramatically when therapy improves or normalizes the EEG [9]. The same may apply in the Landau–Kleffner syndrome (see Chapter 14).

Intermittent and short-lived epileptiform discharges in the EEG may lead to subtle functional impairment, which is only detectable at careful cognitive testing, especially in children with generalized epilepsies. While monitoring the EEG in these patients can be useful in optimizing treatment, it is important to document that suppression of the EEG discharges does result in functional improvement. In fact, there is a risk that any improvement secondary to suppression of such discharges be overshadowed by direct negative effects of the drugs on cognitive function or behaviour. Furthermore, occasionally normalization of the EEG is associated with behavioural deterioration.

Reduction of seizure-related mortality and morbidity

In some cases where seizures are triggered by a treatable cause, such as a brain tumour, removal of the latter is essential to reduce any related morbidity and mortality. In recent years, however, evidence has accumulated that seizures per se are also associated with an increased mortality, partly in relation to accidents which may occur during a seizure and partly in relation to the risk of sudden unexpected death in epilepsy (SUDEP) [2,10]. In patients with frequent convulsive seizures, the incidence of SUDEP may be as high as 1 per 100 or 200 patient-years. Seizures are also associated with an increased risk of physical injuries, particularly burns, head trauma and bone fractures. An effective treatment would be expected to reduce mortality and morbidity, even though this has not been adequately investigated.

Addressing co-morbidities

Many symptomatic epilepsies are aetiologically related to malformative, vascular, neoplastic, degenerative, inflammatory or metabolic disorders which affect the central nervous system, and appropriate management of these conditions must be part of the comprehensive care of these patients.

Neuropsychiatric disorders are also relatively common in patients with epilepsy [11]. In a recent community-based Canadian study of 36 984 individuals, the lifetime prevalence of anxiety disorder was twice as high in people with epilepsy as in those without epilepsy (22.8% versus 11.2%, respectively) [12]. The lifetime prevalence of major depressive disorder and suicidal ideation was 17.4% and 25.0% in people with epilepsy, compared with 10.7% and 13.3%, respectively, in people without epilepsy. Although these co-morbidities have been traditionally regarded as a consequence of the physical and psychosocial limitations associated with seizures, and the adverse effects of antiepileptic drugs, there is increasing evidence that other factors are also involved. In particular, pre-existing depression or a history of suicide attempt have been identified as separate risk factors for incident unprovoked seizures [13].

Many physicians treating epilepsy do not routinely screen for psychiatric disorders, which is regrettable because these co-morbidities may impact on quality of life more than epilepsy and seizures themselves, and therefore need to be identified and treated as appropriate. In a recent study from the USA, the severity of depressive symptoms and the adverse effects of drugs in patients with epilepsy correlated independently with subjective health status, and these factors explained 72% of the variance [14].

Avoidance of adverse drug interactions

Patients receiving therapy with a combination of drugs are at risk for adverse drug interactions, at either the pharmacokinetic or pharmacodynamic level. Drug interactions are not restricted to those resulting from combinations of antiepileptic drugs, but also involve medications taken for other indications [15]. Physicians should be aware of this, and should take all necessary steps to minimize any adverse consequences.

Many drug interactions can be predicted through knowledge of the influence of different drugs on liver drug-metabolizing isoenzymes (see Chapter 28), and in many cases they can be managed with appropriate dosage adjustments and monitoring of plasma drug concentrations. Some antiepileptic drugs have little or no potential for being either a cause or a target of drug interactions, which makes them particularly advantageous in patients requiring multiple drug therapy.

Avoidance of obstruction to patient's life

Therapeutic outcome may be influenced by the patient's ability to identify and avoid situations which could affect susceptibility to seizures, such as excessive sleep deprivation, or – in some photosensitive epilepsies – exposure to intermittent flashing lights or certain video games. While these risk factors need to be discussed and appropriate counselling given, it is equally important to avoid undue restrictions on the patient's lifestyle. For example, alcohol abuse should be actively discouraged, but there is no reason to prohibit one glass of beer or wine at meal times. In general, patients should be encouraged to live a normal life, while avoiding extreme deviations from what would be considered a regular lifestyle.

Prescription of medication should also be aimed at minimizing interference with daily activities. Antiepileptic drugs which can be given once or twice daily are less likely to obstruct daily routines and to cause psychosocial embarrassment, and they are associated with a better compliance. For drugs which can be given once or twice daily but do not have a long half-life, a twice-daily schedule may be preferable because it minimizes the adverse consequences of missing one dose. In general, once-daily dosing does not entail better compliance than twice-daily dosing, but it may have psychological advantages, particularly in patients who are seizure free and perceive each act of pill-taking as the only unpleasant reminder of their disease.

Prevention of epileptogenesis

Experiments in animal models suggest that some antiepileptic drugs not only exert a symptomatic effect by raising seizure threshold, but might also antagonize epileptogenic processes, i.e. the mechanisms through which an epileptic condition becomes established [16]. The suggestion has been made that recurrent clinical seizures may also lead to irreversible neuroanatomical changes which may render the disease more difficult to control, but evidence for this is controversial [17]. If uncontrolled seizure activity leads to the 'chronicization' of the disorder, a case could be made for early and aggressive treatment, and for preferential use of drugs which putatively antagonize epileptogenic processes. Available studies, however, suggest that in most epilepsy syndromes antiepileptic drugs exert merely a symptomatic effect and do not affect the natural course of the disease [18–21]. Admittedly, special conditions may exist in which early effective treatment may improve the ultimate prognosis, possible examples being West syndrome and other early-childhood myoclonic encephalopathies associated with progressive cognitive decline. In the latter conditions, however, the benefit of early seizure control seems to relate more to cognitive outcome than to the history of epilepsy per se [20].

Although not an option at the current state of knowledge, the prevention of epilepsy by using antiepileptogenic drugs in patients at high risk (e.g. after severe head trauma or prolonged convulsive status) may be the ultimate frontier of pharmacological treatment (see Chapter 19). Development of drugs with antiepileptogenic effects could be made easier by advances in the understanding of the molecular mechanisms involved in epileptogenesis. In some conditions, such as tuberous sclerosis, these advances have been truly impressive [22].

When should treatment be started?

The treatment of newly diagnosed epilepsy is discussed in Chapter 10. As emphasized there, a correct diagnosis should be formulated before treatment can be instituted. Differentiation between epileptic and non-epileptic attacks (e.g. psychogenic seizures or syncopal episodes) is not always obvious, and appropriate investigations are required to establish the nature of the disorder. In addition, every effort should be made to identify as early as possible seizure type and syndromic form, because these are important in determining drug selection and prognosis. Although making a syndromic diagnosis is not always easy at the outset, experienced physicians can identify correctly the vast majority of epilepsy syndromes at the very beginning [23]. This is not the case, however, when epilepsy is managed by non-specialists. For example, a recent UK survey of 275 individuals with epilepsy in a deprived area who had no previous contact with the local epilepsy services found that approximately 55% had never received specialist advice, a situation which clearly resulted in suboptimal management [24].

Antiepileptic drug treatment is indicated whenever the expected benefits outweigh potential risks. The risk to benefit equation, in turn, is determined by many factors, including the type of epilepsy, the frequency and severity of the seizures, the age and the occupation of the patient, associated pathological conditions, the characteristics of the drug(s) being considered and the presumed influence of treatment on the patient's well-being and aspirations [1]. These factors are explored in more detail in Chapter 10.

In many situations, the decision on whether to start treatment or to withhold it will involve no uncertainty, but grey areas exist where the optimal therapeutic strategy is uncertain [21]. In any case, the patient should always be involved in the therapeutic decision, because his or her attitude towards the possibility of recurrence of seizures and towards the risks of drug treatment is an important consideration in establishing the indications for treatment.

The actual decision depends on individual factors. A number of different scenarios will be discussed briefly below, and other aspects are covered in Chapter 10.

Patients with a single seizure

The most common situation where there may be uncertainty on whether chronic treatment is justified is when a patient presents with a single unprovoked tonic–clonic seizure whose nature is considered to be probably epileptic [25]. Because many such patients will not have a recurrence when left untreated [26], and because treatment after a first seizure does not improve long-term prognosis [19,21,27], indiscriminate prescription of antiepileptic drugs after a first tonic–clonic seizure, whilst effective in reducing the risk of relapse [21,28], will unnecessarily expose many patients to adverse effects. Therefore, drug therapy is generally deferred until a second seizure occurs. Treatment after a first seizure, however, may be considered when specific prognostic factors indicate a high risk of recurrence (in particular, when the EEG shows interictal epileptiform abnormalities, and/or there is an identified persisting cause for the seizures, such as an MRI-documented cortical dysplasia), when the first unprovoked seizure presented as status epilepticus (suggesting the possibility of an equally prolonged seizure in case of recurrence), or when it is felt that the physical or psychosocial consequences of a seizure recurrence outweigh the risks associated with drug treatment [19,21,25,29,30]. To this purpose, it is essential to fully inform the patient of the implications of starting or withholding treatment, and the patient (or parents) should be involved in the decision process.

The quality of life outcomes of immediate versus deferred treatment in patients with a single seizure or early epilepsy for whom there was uncertainty about the indication for starting treatment was investigated recently in a subcohort of 331 patients in a randomized trial [31]. After 2 years of follow-up, patients randomized to deferred treatment were no more likely to report impairments in general health, cognitive function, psychological well-being or social function than patients assigned to immediate treatment. One area where a difference was identified was driving, where those randomized to deferred treatment were disadvantaged.

Patients with a history of two or more unprovoked seizures

Provided that the epileptic nature of the seizures has been established, patients with recurrent seizures generally require antiepileptic drug therapy [21]. Exceptions may be patients with very minor seizures or rare seizures, particularly when these are mild, brief or occur only during sleep, and do not interfere with daily activities, occupation, psychological state and social integration. Pharmacological treatment is generally not indicated in some benign childhood epilepsies with a self-remitting course, when the adverse effects of antiepileptic drugs are expected to affect quality of life to a greater extent than the seizures themselves (Chapter 14). The best example is represented by children with benign partial epilepsy with centrotemporal spikes (rolandic epilepsy), in whom treatment is usually indicated only in the few cases in whom seizures are frequent, severe and occur during daytime.

Patients with seizures precipitated by specific triggers

When seizures are precipitated by specific triggers, avoidance of the latter may be sufficient. Some forms of photosensitive epilepsy, for example, can be managed by prescribing appropriate lenses, or by instructing the patient on how to avoid exposure to the offending light frequencies. Continuous pharmacological prophylaxis is also not indicated in most children with febrile seizures who are older than 1 year [32].

Other situations

Occasionally, treatment may be justified without a clear diagnosis of epilepsy. When even intensive monitoring fails to provide differentiation between epileptic seizures and pseudo-seizures, a therapeutic trial may be indicated. Lack of response to treatment suggests a non-epileptic nature of the attacks, but it should not be regarded as a conclusive proof for this. Conversely, improvement or even disappearance of seizures after treatment does not prove that the attacks were epileptic in origin. Apart from the possibility of a placebo response or a spontaneous change in the natural history of the disorder, it should be remembered that antiepileptic drugs are not specific in their actions and may influence a wide array of symptoms and signs, including some originating from psychiatric and cardiac diseases. Interpretation of response to treatment is also complicated by the fact that epileptic seizures and pseudo-seizures may co-exist.

It has been argued that under certain circumstances prophylactic treatment may be justified even in the absence of any previous seizure. For example, it has been suggested that in infants with tuberous sclerosis early antiepileptic drug therapy may prevent the occurrence of infantile spasms and, possibly, associated neurological deterioration [1]. Antiepileptic drugs are at times prescribed in the absence of a history of seizures in patients who had a severe head trauma, or those who underwent supratentorial brain surgery, but this practice is not correct. While phenytoin has been found to reduce the risk of early post-traumatic seizures (i.e. seizures occurring in the first 7 days after head trauma) [33], neither phenytoin nor other drugs have been found to be of value in the long-term management of patients with head trauma or brain surgery [18]. In fact, the vast majority of these patients will not develop seizures in the long term and, more importantly, no antiepileptic drug has been found to be effective in reducing the incidence of late post-traumatic or postoperative epilepsy [18].

Initiation of treatment and dose optimization

Rational therapy requires not only choosing the most appropriate drug, but also identifying the optimal dosage [34]. Indeed, one of the most significant advances in the modern treatment of epilepsy has been the recognition that dose requirements vary greatly across individuals, due to pharmacokinetic and pharmacodynamic differences [34]. Optimizing drug choice and dosage are complex processes, and different aspects need to be addressed.

Choice of the most appropriate drug

As a general rule, treatment should be started with a single drug (Table 9.1). To achieve optimal outcome, drug choice should be tailored to ensure the best match between the properties of the medication and the characteristics of the individual. Critical medication-related features include spectrum of efficacy against differ-

ent seizure types, expected magnitude of therapeutic response in the condition of interest, indications and contraindications, characteristics of available formulations, dose escalation and dosing regimen requirements, adverse effects profile, interaction potential, impact on co-morbid conditions, cost and reimbursability. Patient-related factors to be considered include seizure type and syndromic diagnosis, age, gender, co-morbidities, co-medications, risk factors for potential adverse effects (including genotype) and other characteristics such as personal attitudes in relation to possible recurrence or seizures or appearance of specific adverse drug effects. An extensive discussion on how these factors impact on drug selection is provided in Chapter 30.

Dose escalation

When an immediate therapeutic effect is required, as in the management of status epilepticus or frequently recurring seizures, treatment can be started with a loading dose. In most situations, however, this aggressive approach is neither necessary nor desirable, and treatment should be initiated with a small dose and increased gradually to a target maintenance level. Gradual dose escalation has several advantages:

- With most antiepileptic drugs, adaptation (tolerance) to adverse central nervous system and, sometimes, other effects occurs slowly after initiation of treatment [35], and immediate use of a full maintenance dosage may cause major tolerability problems. Drugs which are most likely to produce adverse central nervous system effects when started at doses close to the maintenance dosage include primidone, benzodiazepines, topiramate, tiagabine, vigabatrin, zonisamide and lacosamide. Primidone may cause a particularly marked transient intolerance reaction in patients not previously exposed to barbiturates, and it should be started at a dose (62.5 mg/day in adults) which is only about one-tenth of the usual maintenance dosage [34].
- Despite common belief, allergic and idiosyncratic reactions are often dependent on starting dose and rate of dose escalation [36]. Skin rashes requiring drug withdrawal when treatment is initiated at too-high doses are especially frequent with carbamazepine, phenytoin and lamotrigine. Because valproic acid increases the plasma levels of lamotrigine, the risk of lamotrigine-induced allergic reactions is greatly increased in patients co-medicated with valproic acid, and in these patients it is essential that lamotrigine dosage is escalated at a very slow rate.
- Some patients can be optimally controlled at doses below the initial target maintenance dosage. When seizure frequency is sufficiently high to permit a meaningful assessment of therapeutic response over a short period, slow dose escalation may allow identification of the lowest dose regimen at which patients respond. Conversely, some patients are unusually sensitive to adverse effects, and slow dose escalation will prevent them from being exposed to dosages higher than those tolerated.

Unfortunately, in the case of most antiepileptic drugs, evidence on the optimal rate of dose escalation is limited. Optimal dose titration rates are seldom established in regulatory clinical trials and, therefore, they are mostly identified through postmarketing experience [1]. As shown in Table 9.2, phenytoin, levetiracetam, gabapentin and pregabalin are among the drugs for which the target maintenance dosage can be achieved rapidly without undue toxicity, which is an advantage when latency to onset of therapeutic effects must be minimized. Phenobarbital may also be started at a 'therapeutic' dosage, but because of its long half-life the time-course of pharmacological action is influenced by the slow accumulation of the drug in plasma, a process which may require several weeks. The escalation schemes given in Table 9.2 are only intended for general orientation, and deviations from these recommendations may be indicated in individual cases, or as a result of newly acquired information. Children, elderly patients and patients with certain co-morbidities or co-medications may require doses and titration rates different from those given in the table [34]. The rate of dose escalation is also partly dependent on the treatment setting: a patient with frequent seizures, for example, may require more rapid dose escalation than a patient with infrequent seizures.

Table 9.1 Advantages of monotherapy.

High efficacy (complete seizure control in the majority of patients)
Better tolerated than multiple drug therapy
Easy management (efficacy and safety of individual drugs can be evaluated separately)
Simple (possibly better compliance)
No adverse drug interactions
Cost-effective

Initial target maintenance dosage

The initial target maintenance dosage can be defined as the dosage at which the patient is stabilized at the end of the initial dose escalation phase [34]. In general, this corresponds to the lowest daily dosage which is expected to produce seizure control in that individual patient. This approach is justified by the desire to minimize the probability of exposing patients to long-term treatment with dosages higher than necessary.

In recent years, evidence has accumulated that most patients with newly diagnosed epilepsy who achieve seizure freedom on the initially prescribed drug do so at relatively low doses, and only a small group necessitates doses in the medium to high range. In a large single-centre study which explored the effectiveness of the first prescribed antiepileptic drug, the majority of patients who became seizure free were controlled at doses of 400–600 mg/day for carbamazepine, 600–1000 mg/day for valproate and 125–200 mg/day for lamotrigine [7]. In a recent randomized trial that compared carbamazepine and levetiracetam in adults with newly diagnosed partial epilepsy, about 90% of seizure-free patients were controlled at doses of 400 mg/day for carbamazepine and 1000 mg/day for levetiracetam [37].

An indication of possible initial target maintenance dosages is provided in Table 9.2. In practice, the target dosage should be individualized based on expectations concerning the patient's responsiveness to the drug. Many idiopathic generalized epilepsies respond well to treatment, and it may be justified in these patients to aim at initial maintenance dosages and plasma drug levels in the low range. For example, the dosage of valproic acid required to control primary generalized tonic–clonic seizures has been found to be about 30% lower than that required to control partial seizures [38]. A high seizure frequency before starting

Table 9.2 Suggested initial target maintenance dosages, frequency of administration and titration rates for the main antiepileptic drugs in adults.

Drug	Usual initial target maintenance dosage (mg/day)	Usual maintenance dosage (mg/day)	Frequency of administration	Suggested titration rate
Carbamazepine	400–600[a]	400–1600	2 to 3 times/day (twice daily with controlled-release formulations)	Start with 100 or 200 mg/day and increase to target dosage over 1–4 weeks
Clobazam	10	10–30	Once or twice daily	Start with 10 mg/day. If indicated, increase to 20 mg/day after 1–2 weeks
Ethosuximide	500–750[a]	500–1500	2 to 3 times/day	Start with 250 mg/day and increase to target dosage over 1–3 weeks
Felbamate	1800–2400	1800–3600	3 or 4 times/day	Start with 600–1200 mg/day and increase to target dosage over 10–21 days
Gabapentin	900–1800	900–3600	2 or 3 times/day	Start with 300–900 mg/day and increase to target dosage over 5–10 days
Lamotrigine	50–150 (monotherapy); 50–100 (patients on valproic acid); 200–300 (patients on enzyme inducers)	50–200 (monotherapy or patients on valproic acid); 200–500 (patients on enzyme inducers)	Twice daily (once daily possible with monotherapy and valproic acid co-medication)	Monotherapy: start with 25 mg/day for 2 weeks, then increase to 50 mg/day for 2 weeks. Further increases by 50 mg/day every 2 weeks Valproic acid co-medication: start with 25 mg on alternate days for 2 weeks, then 25 mg/day for 2 weeks. Further increases by 25–50 mg/day every 2 weeks Enzyme-inducing co-medication: start with 25 or 50 mg/day for 2 weeks, then increase to 50 or 100 mg/day for 2 weeks. Further increases by 50–100 mg/day every 2 weeks
Lacosamide	200–400	200–400	Twice daily	Start with 100 mg/day and increase to target dosage by increments of 100 mg/day every week
Levetiracetam	1000–2000[a]	1000–3000	Twice daily	Start with 500 or 1000 mg/day and increase, if indicated, after 2 weeks
Oxcarbazepine	600–900[a]	600–3000	2 or 3 times/day	Start with 300 mg/day and increase to target dosage over 1–3 weeks
Phenobarbital	50–100[a]	50–200	Once daily	Start with 30–50 mg at bedtime and increase, if indicated, after 10–15 days
Phenytoin	200–300[a]	200–400	Once or twice/day	Start with 100 mg/day and increase to target dosage over 3–7 days
Pregabalin	150–300	150–600	2 or 3 times/day	Start with 75 mg/day for 3 days, then increase to 150 mg/day. If indicated, increase to 300 mg/day after 2 weeks
Primidone	500–750[a]	500–1500	2 or 3 times/day	Start with 62.5 mg/day and increase to target dosage over about 3 weeks. In patients on enzyme-inducing co-medication a faster titration may be used
Rufinamide	1200	1200–3200	Twice daily	Start with 400 mg/day and increase by 400 mg/day increments every 2–4 days
Tiagabine	30 (patients on enzyme inducers); 15 (patients not on enzyme inducers)	30–50 (patients on enzyme inducers); 15–30 (patients not on enzyme inducers)	2 to 4 times/day	Start with 5 mg/day and increase by 5 mg/day increments at weekly intervals
Topiramate	100[a]	100–400	Twice daily	Start with 25 mg/day and increase by 25 or 50 mg/day increments every 2 weeks
Valproic acid	500–1000[a]	500–2500	2 or 3 times/day (once or twice daily with controlled-release formulations)	Start with 500 mg/day and increase, if indicated, after about 1 week
Vigabatrin	1000	1000–3000	Once or twice daily	Start with 250 or 500 mg/day and increase to target dosage over 1–2 weeks
Zonisamide	200	200–500	Twice daily	Start with 50 mg/day, increase to 100 mg/day after 1 week and to 200 mg/day after 1 further week

From ref. 34.

This information reflects the author's assessment of available evidence and may differ from information reported in data sheets in individual countries. Some patients will require dosages, titration rates and dosing regimens different from those given in this table.

[a] Suggested target dosage for initial monotherapy in patients with newly diagnosed epilepsy. For some drugs, larger target dosages may be appropriate in refractory patients.

therapy, symptomatic epilepsy, partial seizures, multiple seizure types, associated neurological handicaps and an unfavourable response to previous antiepileptic drug therapy all influence the prognosis negatively [39,40], and patients with these features are expected to require comparatively higher doses and plasma drug levels. Other factors affecting choice of the initial maintenance dosage include the presence of physiological or pathological conditions leading to altered drug disposition [41–44], and any co-medication expected to interact pharmacokinetically or pharmacodynamically with the drug to be administered [15]. Elderly patients, in particular, generally require dosages in the low range, since they exhibit an increased sensitivity to the effects of antiepileptic drugs [45,46].

The patient's attitude should also be considered. A higher maintenance dosage is justifiable wherever recurrence of seizures is expected to have a particularly severe psychological or social impact on the individual's life. Some neurologists also favour the use of relatively high initial maintenance dosages out of fear that a delay in achieving complete seizure control may increase the probability of the epilepsy becoming intractable. However, as discussed earlier in this chapter, at least for most of the epilepsy syndromes, there is no evidence that this is the case.

Frequency of administration

For most antiepileptic drugs, attainment of an adequate response is dependent on the persistence of efficacious drug concentrations at the site of action in the brain. Because the concentration at the site of action is in equilibrium with the concentration in plasma, a dosing scheme should be used which is adequate to maintain relatively stable plasma drug concentrations throughout a 24-h period [47].

The degree of fluctuation in plasma drug concentration during a dosing interval is dependent on the duration of such interval, the rate of absorption of the drug and its elimination half-life. With rapidly absorbed compounds, it is a good general rule to choose a dosing interval which is no greater than the half-life of the drug. Drugs with a slow elimination rate such as phenobarbital may be given once daily at bedtime, but most other antiepileptic drugs need to be given two or three times daily. The optimal frequency of administration may also vary depending on pharmacokinetic patterns in different patient groups. For example, lamotrigine should be given twice daily in patients taking concomitant enzyme-inducing anticonvulsants (due to its relatively short half-life in these patients), but it may be given once daily in adults receiving no co-medication, and, even more appropriately, in those co-medicated with valproic acid, which prolongs the half-life of lamotrigine.

For short half-life compounds such as carbamazepine and tiagabine, more than two daily administrations may be required to minimize excessive fluctuations in plasma concentration. This is especially important for patients in whom half-lives are at the shorter end of the spectrum, such as children and enzyme-induced individuals [34]. With these drugs, intermittent adverse effects are not uncommon at the time of peak drug concentration, whereas breakthrough seizures may occur when plasma drug levels fall below a critical threshold. More than twice-daily dosing may similarly be required for gabapentin, which also has a short half-life and, additionally, is absorbed from the intestine by a saturable transport mechanism [47]. Particularly in patients receiving high dosages, utilizing multiple daily administrations of gabapentin provides a strategy to improve the oral absorption of the drug. To minimize the inconvenience of multiple daily dosing and to improve compliance, extended-release formulations suitable for twice-, and in some cases, once-daily dosing have been developed for a number of drugs [48]. These are discussed briefly in the next section of this chapter.

In some patients, even drugs with short half-lives such as gabapentin and tiagabine may still produce adequate responses with a twice-daily schedule. This may be explained, at least in part, by pharmacodynamic variability, i.e. the fact that some patients may tolerate well high peak plasma drug levels or, conversely, maintain a good response at low trough concentrations. For some drugs, there is also evidence that a dissociation exists between their concentration profile in plasma and the duration of effect. For example, levetiracetam is recommended for use on a twice-daily schedule despite a plasma half-life of about 7 h. In the case of vigabatrin, which also has a plasma half-life of about 7 h, even once-daily dosing may be appropriate due to the fact that its action involves irreversible inhibition of GABA transaminase, and therefore duration of effect is dependent more on the turnover rate of the enzyme than on the chemical half-life of the drug in plasma [49]. There is some evidence that valproic acid also has a longer duration of action than expected from its half-life [50], and once-daily dosing of valproate is feasible in many patients, particularly when a sustained-release formulation is used. Once-daily valproic acid, however, is not recommended in women of childbearing potential, because animal studies suggest that teratogenic effects may be enhanced at high peak plasma concentrations of the drug [51].

Choosing among different formulations (including generics)

For patients stabilized on chronic treatment, tablets or capsules should be preferred to syrups, whenever possible, because they allow more precise dosing, avoid the effect of tooth-damaging ingredients such as sucrose, and minimize the risk of adverse effects associated with excessively rapid absorption. Nearly all children above the age of 5 years can cope with conventional solid dosage forms. For some drugs, solid dose forms designed especially for infants and younger children (e.g. powders, sprinkles and granules) have also been made available. The type of formulation influences the rate of drug delivery to the bloodstream and, hence, to the site of action. Enteric-coated tablets, such as those utilized in some formulations of valproic acid, can be absorbed only after the tablet reaches the intestine, and therefore absorption shows a lag-time related to the rate of gastric emptying. Typically, the passage of enteric-coated tablets to the intestine is delayed by the concomitant ingestion of food, and, therefore, when enteric-coated formulations are administered with a meal, drug absorption may not take place for up to many hours after the ingestion [47].

In most countries, different formulations of the same drug are available, and some of these may differ in bioavailability. Switching between products with different bioavailability (for example, switching from a regular to a modified-release product, or between other products known not to be bioequivalent) may result in a

change in plasma drug levels and, consequently, in loss of seizure control or clinical toxicity. To minimize risks, switches between these products should be done only when necessary, clinical response should be monitored carefully and, whenever possible, plasma drug concentrations should be measured to determine whether dose adjustments are needed.

In recent years, generic products of antiepileptic drugs have been introduced in most countries. Current regulations concerning the approval of generics are strict, at least in Europe and the USA, and require that the plasma concentrations of the active principle after intake of the generic be equivalent to those measured after intake of the brand [52]. In practice, bioequivalence is established by demonstrating that 90% confidence limits for the ratio of key pharmacokinetic parameters after intake of the generic and brand product fall within the 80–125% range. For those confidence limits to be met, however, mean estimates for ratios of measures of rate and extent of absorption must be relatively close to 100%. There has been considerable debate about benefits and risks associated with generic prescribing [52,53]. Generics bring major cost benefits to individuals and to society, but concern has been expressed that conventional confidence limits for bioequivalence may be too wide for antiepileptic drugs, and that even a modest reduction in plasma drug concentration after switching to/from a generic may be sufficient to cause recurrence of seizures in occasional patients. Moreover, it has been pointed out that while each generic has to be bioequivalent to the corresponding brand, bioequivalence is not guaranteed when switching from a generic to another [52]. In view of these considerations, there is general agreement that any switch between pharmaceutical products of antiepileptic drugs should be approved by the physician, that switches between different generics should be avoided whenever possible, and that there may be special categories of patients (particularly those who are seizure free) in whom switches may be generally undesirable [52,53]. Greater concerns apply to countries in which regulatory control of the quality of pharmaceuticals is less strict, particularly in the underprivileged world [54]. Monitoring plasma concentrations can be useful for rapid detection of potential changes in plasma drug concentration when switching formulations.

Sometimes, it is desirable to modify a drug's rate and extent of absorption in order to obtain a more favourable plasma concentration profile. In particular, for drugs which are absorbed and eliminated rapidly, sustained-release preparations have been developed which are designed to prolong the absorption, produce a smoother drug concentration profile and allow less frequent dosing [48]. Modified-release products are currently available for carbamazepine, valproic acid, phenytoin, lamotrigine, oxcarbazepine and levetiracetam. These formulations can be administered conveniently twice daily, and some are also suitable for once-daily dosing. With once-daily dosing, however, the advantages of improved convenience should be weighed against the risks associated with a prominent decrease in plasma drug levels should the patient forget to take one dose [48]. At least for some drugs, most notably carbamazepine, sustained-release formulations provide clear advantages, particularly in reducing intolerability associated with excessively high peak plasma concentrations [46,48]. It should be noted, however, that some modified-release formulations may differ from conventional formulations not only in rate, but also in extent of absorption. Therefore, an adjustment in total daily dosage may be needed when switching from a conventional to a modified-release formulation or vice versa.

In certain situations, routes of administration other than the oral route may be indicated, and appropriate formulations will then be needed. When an immediate effect is required, such as in the treatment of status epilepticus, the intravenous route is preferred whenever feasible (see Chapter 18). Intramuscular administration of drugs such as phenytoin, phenobarbital and diazepam is generally not recommended, because absorption may be slow and poorly predictable. Midazolam and fosphenytoin, on the other hand, are absorbed efficiently when given intramuscularly. In the case of diazepam, the rectal route provides rapid and efficient absorption when solutions, gels or rectal capsules are used, and can be utilized by non-medical personnel in selected situations, for example to prevent or terminate a seizure in a febrile child. With midazolam, the buccal and the intranasal routes may also ensure rapid absorption, and have been used for rescue therapy in seizure patients [55]. Formulations suitable for alternative routes of administration are also desirable to substitute for oral medication in patients unable to take a medicine orally, for example after abdominal surgery.

Adjusting dosage in patients not responding to the initial target dosage

According to pharmacokinetic principles, about five half-lives are required to reach steady-state plasma concentrations after stabilizing the patient on a given dosage [47]. Response to treatment cannot be fully evaluated before this period, and this should be taken into account in determining the minimum interval which should elapse before assessing the need for dosage adjustments. For drugs such as valproic acid and carbamazepine, which have relatively short half-lives, steady-state conditions are achieved within a few days (Table 9.3), whereas for phenytoin and phenobarbital it may take weeks for the plasma concentration to stabilize following a dose change. There are instances of patients who have been discharged from clinical observation too soon after a dose increment and became subsequently intoxicated as a result of progressive drug accumulation.

In patients who continue to have seizures after stabilization at the initial target dose, dosage should be increased stepwise within the recommended range until seizures are controlled or until intolerable adverse effects appear. The magnitude of dosage increments should be determined by the steepness of the dose–response relationship, which varies between drugs, and by the patient's response at the previously assessed dose. Particular care should be taken when adjusting phenytoin dosage, because small dose increments can result in disproportionate increase in plasma drug levels [56]. Although most physicians are aware of the need for careful individualization of dosage, inadequate dosing remains an important determinant of suboptimal seizure control. In a study of 74 consecutive patients referred for epilepsy surgery to a tertiary level centre in Germany due to 'medical intractability', careful evaluation of medical history revealed that these patients had not been exposed to maximally tolerated doses of carbamazepine, phenytoin or barbiturates [57]. When the same patients were rechallenged with appropriate doses of one or more of these drugs, seven showed such a major improvement in seizure control

Table 9.3 Elimination half-lives of antiepileptic drugs and time to reach steady-state plasma drug concentrations in adults. Half-lives may be longer in newborns and shorter in infants and children.

Drug	Half-life		Time to reach steady state (days)	Comments
	Patients not taking enzyme inducers[a]	Patients taking enzyme inducers[a]		
Carbamazepine	8–25 h	5–15 h	2–7 days	Owing to autoinduction, plasma drug levels may decline after about 14 days of initiation of treatment
Clobazam	10–30 h	8–16 h	2–6 days	Active demethylated metabolite with longer half-life requires about 10 days to reach steady state
Clonazepam	20–60 h	10–35 h	2–10 days	
Ethosuximide	40–60 h	20–40 h	4–10 days	
Felbamate	14–23 h	10–18 h	2–4 days	
Gabapentin	5–7 h	5–7 h	2 days	
Lamotrigine	15–35 h	8–20 h	2–6 days	In patients comedicated with valproic acid, half-life is longer (40–80 h) and steady state may not be reached until 7–15 days
Lacosamide	12–16 h	12–16 h	2–4 days	
Levetiracetam	6–8 h	4–8 h	2 days	
Oxcarbazepine	8–15 h	7–12 h	2–4 days	Data refer to the metabolite monohydroxy-carbazepine, for which oxcarbazepine can be considered a prodrug
Phenobarbital	50–170 h	50–170 h	8–30 days	
Phenytoin	10–100 h	10–100 h	4–20 days	Half-life and time to reach steady state increase with increasing dosage
Pregabalin	5–7 h	5–7 h	2 days	
Primidone	10–20 h	5–10 h	2–4 days	Most of the pharmacological effects are mediated by the metabolite phenobarbital, which may require 8–30 days to reach steady state
Rufinamide	6–10 h	6–8 h	2 days	
Tiagabine	4–13 h	2–4 h	2 days	
Topiramate	20–30 h	10–15 h	2–5 days	
Valproic acid	11–20 h	6–12 h	2–4 days	
Vigabatrin	5–8 h	5–8 h	2 days	
Zonisamide	50–70 h	25–35 h	5–12 days	

[a] Enzyme inducers include carbamazepine, phenytoin, phenobarbital and primidone.

that their surgery programme was cancelled. Admittedly, it may be difficult to reach consensus on what is a maximally tolerated dosage in an individual patient, as this is influenced by both physician's and patient's perceptions. In particular, the acceptability of adverse effects depends on the patient's lifestyle priorities; for example, age and occupation will influence a patient's reaction to the modest cognitive impairment or verbal slowness which can be associated with some treatments. If individual preferences are not addressed adequately, the patient may find it difficult to adhere to the prescribed dosing regimen.

The need to adjust dosage in uncontrolled patients cannot be disputed, and the therapeutic potential of any given drug should be fully explored before switching to alternative treatments. However, there should be no overexpectations of outcomes achievable with high-dose therapy. In fact, only a modest proportion of patients who fail to respond to doses in the low to medium range will achieve seizure freedom at higher doses [7,37], and even subsequent treatments with alternative drugs will not produce high seizure freedom rates in these patients [39,58]. It should also be recognized that the efficacy of antiepileptic drugs does not always increase with increasing dosage. Too-large dosages, or simultaneous prescription of too many drugs, may lead to a paradoxical increase in seizure frequency [59]. The physician should be aware of this possibility, because failure to recognize drug-induced seizure aggravation may lead to further increase in drug load and consequent clinical worsening.

Monitoring plasma drug concentrations can be useful in deciding the need and magnitude of dosage adjustments [60]. However, dose adjustments should be based primarily on clinical response and patients who are seizure free at low plasma drug concentrations should not have their dosage increased. Conversely, since some patients may tolerate and indeed require plasma drug concentrations above the upper limit of the reference range, no patient should be considered drug resistant unless seizures continue at the maximal tolerated dosage (within the clinically used dose range), irrespective of plasma drug concentrations.

Dose optimization in special situations

The strategy concerning dose titration used in children is similar to that described for adults, although some severe conditions, such as West syndrome, may dictate more aggressive dose escalation. Since drug clearance for most antiepileptic drugs is higher in infants and children than in adults [41,42], dosage requirements on a milligram per kilogram basis are usually higher in paediatric patients than in adults (Table 9.4). Conversely, newborns, especially when born prematurely, often have a reduced drug clearance and therefore may require lower dosages. During chronic treatment in children, dosage is rarely modified based on

Table 9.4 Suggested maintenance dosages of AEDs in infants and children.

Drug	Maintenance dosage for infants (mg/kg/day)	Maintenance dosage for children (mg/kg/day)
Carbamazepine	10–40[a]	5–30
Clobazam	0.5–1	0.25–0.75
Clonazepam	0.1–0.2	0.05–0.1
Ethosuximide	20–40	15–45
Felbamate	20–60	15–45
Gabapentin	ND	10–30
Lacosamide	ND	ND
Lamotrigine	ND	1–5 (valproate co-medication) 5–15 (enzyme-inducing co-medication)
Levetiracetam	ND	10–60
Oxcarbazepine	15–60	10–50
Phenobarbital	3–5	2–4
Phenytoin	5–15[a]	5–9
Pregabalin	ND	ND
Primidone	ND	5–25
Rufinamide	ND	[c]
Tiagabine	ND	ND
Topiramate	ND	1–5
Valproic acid	20–40[b]	10–30[b]
Vigabatrin	80–150	40–80
Zonisamide	ND	4–12

Modified from ref. 34.

This information reflects the author's assessment of available evidence and may differ from information reported in data sheets in individual countries. Some patients will require dosages different from those given in this table.

ND, no adequate data available or not approved in this age group.

[a] Bioavailability may be poor in infants.

[b] Higher dosages may be needed in patients comedicated with enzyme inducers.

[c] Rufinamide doses approved in Europe are 200–1000 mg/day for patients without valproate co-medication weighing <30 kg, 200–600 mg/day for patients comedicated with valproate weighing <30 kg, and 400–1800 mg/day for patients weighing 30–50 kg.

body weight changes alone, and assessment of clinical response is essential in determining the need for dose adjustments [34]. Compared with adults, children are more often treated with liquid dosage forms, which show faster rates of absorption than tablets or capsules. Coupled with the shorter half-life of many drugs in children, this results in amplified fluctuations in plasma drug levels, often necessitating more frequent daily dosing to avoid intermittent adverse effects.

At the other extreme of age, in the elderly, dosage may need to be adjusted to compensate for reduced renal and hepatic drug clearances [41]. Binding of drugs to plasma proteins may be altered in elderly people with hypoalbuminaemia, and consequently total plasma drug concentrations may underestimate the levels of unbound, pharmacologically active drug in these patients. In general, epilepsy in the elderly tends to respond to lower dosages than those used in younger patients, but the elderly also show an increased susceptibility to adverse effects [44–46].

Associated diseases, particularly those affecting the liver and the kidney, may alter dosage requirements to a major extent [43,44]. Patients with associated diseases are also more likely to take concomitant medications, with the attendant risk of drug interactions (Chapter 28).

Assessing clinical response

Under usual circumstances, assessment of therapeutic response is based on direct observation of seizures. Patients or their relatives should be provided with a diary and instructed to record seizures carefully, utilizing simple codes which allow differentiation by seizure type. In addition to dates on which seizures occur, it may be useful to include in the diary information on the actual timing of the seizures (e.g. nocturnal, awakening or diurnal seizures) and events potentially affecting seizure susceptibility, i.e. menstrual periods, situations leading to sleep deprivation, and days on which medication was missed or taken incorrectly. When assessing the effect of therapy on seizure frequency, consideration should be given to whether plasma drug levels had reached steady-state conditions after a change in dosage. Baseline seizure frequency also needs to be considered: if at baseline a patient experienced only one seizure every 2 or 3 months, it may take up to 1 year to determine with reasonable confidence whether a change in drug therapy led to seizure freedom. As discussed earlier in this chapter, efficacy should not be established by assessing changes in the EEG: however, EEG recordings may be useful or even required to assess drug response in special situations, e.g. in status epilepticus (particularly when anaesthesia has been applied and there is no other method to determine ongoing electrical activity in the brain), in patients with absence seizures and wherever subclinical EEG paroxysms cause functional impairment.

It is essential that the patient be monitored carefully not only for seizure activity, but also for potential co-morbidities (particularly psychiatric conditions) and adverse drug effects [4,61]. This can be done by interviews and examinations at appropriate intervals. Since important adverse effects are easily overlooked, the use of simple, self-administered questionnaires can be of great value in screening patients for potential toxicity, and have been shown to improve substantially clinical outcome [8]. Likewise, the patient and the family should be informed about adverse effects that may be anticipated and any action that may have to be taken, particularly with respect to early signs of serious toxicity.

Routine haematology and blood chemistry tests should be obtained before starting treatment, and repeated at least once during treatment and when another drug is added or substituted. While more frequent laboratory safety monitoring may be recommended for certain drugs (most notably, felbamate), the most efficient strategy for identifying serious adverse effects is to alert patients about the need to report immediately any warning symptoms and signs [36,62]. In particular, bleeding, bruising and infections may be early manifestations of blood dyscrasias, whereas profound asthenia, marked sedation, vomiting, fever and increased seizure frequency should alert about the possibility of valproic acid-induced liver toxicity. Special safety tests are required in special circumstances: patients started on vigabatrin, for example, must have their visual fields tested regularly by Goldman perimetry. The value of monitoring plasma drug concentrations as an

aid to improve clinical response is discussed later in this chapter.

What next when the initial treatment fails?

The treatment of chronic and active epilepsy is discussed further in Chapter 11, but here a number of general aspects are covered, which apply to epilepsy at all stages in its evolution.

When seizures continue at the maximally tolerated dose of an antiepileptic drug, a care review is indicated. First, it is important to confirm that the diagnosis was correct, that the initial treatment was appropriate and that there are no removable causes of inadequate response (e.g. poor compliance, sleep deprivation or alcohol abuse). After excluding these sources of poor response, the best strategy in most cases is to substitute the first drug with a second, also given as monotherapy. As discussed below, monotherapy with an alternative drug will produce seizure control in an appreciable number of patients, and is likely to be better tolerated than combination therapy [4,39,58]. Early combination therapy, however, may be preferred in selected cases, for example in patients with severe epilepsies who showed a favourable but incomplete response to the initially prescribed drug and are considered unlikely to achieve seizure freedom on an alternative monotherapy. Trials of combination therapy are also justified in patients who failed two or more sequential monotherapies. The probability of achieving sustained seizure freedom after failing to respond at maximally tolerated dosages of three or more antiepileptic drugs is much less than in newly diagnosed patients, but even in chronic established epilepsy, a significant minority of patients will respond at least to some extent (this is discussed further in Chapter 11). Where epilepsy is severe and intractable, early consideration should be given to the feasibility of epilepsy surgery.

Alternative monotherapy

As summarized in the preface of this book, the vogue for antiepileptic drug monotherapy dates from the late 1970s and the advantage of monotherapy over combination therapy has been stressed many times since. The first formal trial comparing alternative monotherapy with combination therapy was conducted by Hakkarainen [63], who randomized 100 patients with newly diagnosed convulsive seizures to either carbamazepine or phenytoin. The 50 patients who continued to have seizures after 1 year on the allocated treatment were switched to monotherapy with the alternative drug and, of these, 17 (34%) became seizure free. On the other hand, of the 33 patients who were refractory to *both* phenytoin and carbamazepine as monotherapy, only five (15%) could be controlled when the two drugs were given together. While the value of combination therapy in this trial may have been underestimated due to the fact that carbamazepine and phenytoin, sharing similar mechanisms of action and adverse effect profiles, are probably not the best drugs to use together, the study clearly showed that alternative monotherapy is a valuable option in patients refractory to initial treatment. This finding has been confirmed repeatedly. In a large observational study in which a variety of drugs were used, 67 of 248 patients (27%) refractory to initial monotherapy were rendered seizure free with a second or third drug used as monotherapy, and only 12 were controlled by combination therapy [39]. In a more recent pragmatic controlled trial, 157 patients with refractory partial epilepsy not controlled after single ($n = 94$) or sequential monotherapies were randomized to monotherapy with an alternative drug or to combination therapy by adding a second drug [64]. The 12-month probability of remaining on the assigned treatment was 55% in patients randomized to alternative monotherapy, and 65% on those randomized to adjunctive therapy, a non-statistically significant difference. The 12-month probability of remaining seizure free in the two groups was 14% and 16% respectively. Although the statistical power of the study was limited by the relatively small sample size, these results reinforce the evidence that success rates on combination therapy are not much greater than those achieved with alternative monotherapy. In the latter trial, adverse effects rates associated with monotherapy were not lower than those reported with combination therapy. However, in other studies where patients refractory to initial treatment were switched to combination therapy, the burden of adverse effects was greater with polytherapy than with monotherapy [65].

Based on the above evidence, switching to an alternative monotherapy seems to be the best strategy in the majority of patients unresponsive to initial treatment. While it could be argued that addition (rather than substitution) of a second drug will allow more rapid achievement of seizure control in those few patients who do require combination therapy, such a policy has the drawback of exposing to a greater burden of adverse effects many patients who can be managed with a single drug. In practice, to minimize the risk of withdrawal seizures, it is preferable to avoid abrupt discontinuation of pre-existing medication when switching to an alternative drug. Many physicians prefer to titrate the dosage of the second agent up to the maintenance level before starting the gradual withdrawal of the initial medication. This procedure offers the advantage of minimizing the risk of seizure worsening during the switch-over phase, although there is a drawback in that the patient may be exposed to a greater risk of adverse drug interactions during the addition or discontinuation phase. An alternative strategy is to decrease gradually the dosage of the initial drug whilst substitution therapy is being introduced, although this may involve a greater risk of seizures during the switch-over phase. Some drugs, particularly benzodiazepines, carbamazepine, barbiturates, phenytoin and vigabatrin, should be withdrawn with special caution, taking into consideration the previous duration of exposure and the pre-existing dosage of these drugs, with at least 2–3 months being usually advisable to complete the withdrawal [34].

A therapeutic strategy which is intermediate between alternative monotherapy and combination therapy involves adding initially a second drug, stabilizing the patient for a period sufficient to assess response to combination therapy at optimized dosages, and then proceeding with gradual removal of the initial drug if a good response has been achieved. If the patient needs the drug combination to remain seizure free, this will become readily apparent and the withdrawal procedure can be rapidly reversed. While apparently attractive, this procedure has drawbacks. It exposes the patient to the risk of adverse drug interactions and to the adverse effects of prolonged polytherapy. Furthermore,

many patients who become seizure free will be unwilling to take any risks associated with a treatment change, and may therefore elect to continue to take a pharmacological load which is possibly greater than necessary.

Combination therapy

As discussed above, combination therapy should be preferably reserved for patients refractory to two or more sequential monotherapies, even though earlier, more aggressive utilization of polypharmacy may be justified in occasional cases, for example in severe and notoriously refractory epilepsy syndromes. The usefulness of adding a second, and sometimes even a third, drug in patients with refractory epilepsy is well documented by long-standing clinical experience and by the results of many placebo-controlled add-on trials [66], even though it cannot be excluded that in some trials an improvement in seizure frequency could have been obtained simply by increasing the dosage of baseline medication or by switching to an alternative monotherapy. In general, between 20% and 50% of patients with chronic refractory epilepsies show at least a 50% reduction in seizure frequency after adding a second or third drug [66,67], but the actual proportion achieving seizure freedom is considerably smaller (less than 20%) [68].

When another drug is added on, pharmacokinetic and/or pharmacodynamic interactions may occur, leading to the need for dosage adjustments (Chapter 28). For example, valproic acid inhibits the metabolism of lamotrigine and phenobarbital, and a reduction in the dosage of the latter drugs is usually indicated when valproic acid is added on [69]. Most pharmacokinetic interactions can be identified and managed by monitoring plasma drug concentrations, but measurement of drug levels is of no value when the interaction is pharmacodynamic. One example of adverse pharmacodynamic interaction is provided by the appearance of symptoms suggestive of carbamazepine toxicity in some carbamazepine-treated patients started on adjunctive treatment with lamotrigine. These symptoms are not usually associated with any change in the plasma concentration of carbamazepine or carbamazepine-10,11-epoxide, though they generally disappear after a reduction in carbamazepine dosage [70].

While the value of combination therapy in selected patients (albeit a minority of all patients) is unquestionable, the risk of overtreatment is significant [4] and a common problem in epilepsy practice. Polytherapy, especially when high dosages are used, involves a greater burden of adverse effects, and the overall impact on the patient's quality of life must be closely scrutinized. It should also be remembered that in patients with chronic refractory epilepsy, any beneficial effects following a change in treatment may be more apparent than real. In fact, these patients typically show wide fluctuations in seizure frequency over time, and it is not uncommon for an antiepileptic drug to be added during a period of spontaneous exacerbation: under these conditions, the subsequent improvement in seizure frequency may be related to spontaneous amelioration (the phenomenon of regression to the mean) rather than to the effect of the added drug [71]. Because of this, the need for maintaining combination therapy should be reassessed at regular intervals, and monotherapy should be re-instituted whenever appropriate. Furthermore, as mentioned above, an excessive drug burden created by drug combinations may also lead to a paradoxical deterioration in seizure control. In many patients who fail to achieve sustained benefit from an added drug, restoration of monotherapy may result not only in relief from adverse effects but also, sometimes, in improved seizure control.

Are some drug combinations more useful than others ('rational polytherapy')?

The possibility exists that two antiepileptic drugs interact pharmacodynamically by enhancing reciprocally their seizure-suppressing effects, without any potentiation of their toxicity. In animal experiments, some drug combinations do show a better therapeutic index than others, but the clinical relevance of these findings is difficult to assess [72]. Although the suggestion has been made that combining antiepileptic drugs with different mechanisms of action should be beneficial [73], current knowledge of the modes of action of the various drugs, most of which have more than one primary action, is insufficient to allow a rational application of this principle [72]. Therefore, drugs are usually combined on empirical grounds. In particular, it is generally desirable, whenever possible, to use combinations of drugs with different (or, possibly, even antagonistic) adverse effects, and to avoid drugs associated with major adverse interactions. The term 'rational polytherapy' has been coined, although there is nothing particularly rational about the choices made, and the term has a greater marketing than scientific value.

In general, there is meagre clinical evidence in favour of any particular combination. The best documented useful combinations are valproic acid plus ethosuximide in the management of refractory absence seizures [74] and valproic acid plus lamotrigine in a variety of refractory seizure types [69,73,75]. The latter combination also has minor pharmaco-economic advantages, because valproic acid inhibits lamotrigine metabolism and reduces the dosage requirements (and associated cost) of the latter. However, because of the risk of pharmacokinetic interactions, the use of the lamotrigine–valproic acid combination requires special caution, and care must be taken that the lamotrigine dosage is escalated slowly in these patients. The dosage of valproic acid may also need to be adjusted to optimize efficacy and tolerability, and further adjustments in lamotrigine dosage are likely to be required should valproic acid be discontinued.

Monitoring plasma drug concentrations as a tool to improve therapeutic outcome

The pharmacokinetics of most antiepileptic drugs exhibits marked inter-individual variation, resulting in large differences in plasma drug concentrations at steady state among patients receiving the same dose. Since the drug concentration in plasma is in equilibrium with that in the brain, this variability affects the degree of pharmacological response, and therapeutic and toxic effects are expected to correlate better with the drug concentration in plasma than with the prescribed daily dose [60]. Based on this background, monitoring plasma drug concentrations ('therapeutic drug monitoring') has been found to provide a useful guide to adjusting dosage of many antiepileptic drugs.

In practice, therapeutic drug monitoring requires considerable interpretative skills [76], and physicians should always adhere to

the principle that therapeutic decisions must be based primarily on evaluation of clinical response rather than drug measurements alone. The use of plasma drug levels in the treatment of epilepsy is discussed comprehensively in a recent position paper of the International League Against Epilepsy (ILAE) [60], and only basic concepts are outlined below.

When should blood samples be taken?

In general, blood samples for drug measurements should be taken at steady state, i.e. when at least five half-lives have elapsed since the last dose change. For drugs with a long half-life, such as phenobarbital, the daily fluctuation in plasma concentration is negligible and the exact time of sampling is not important. With other compounds, it is preferable to collect the sample in the morning before the first daily dose, when the concentration is usually at its trough. For drugs exhibiting significant variation in plasma concentration during the dosing interval, such as carbamazepine and valproic acid, it is at times useful to obtain a second sample at the time of the expected peak concentration, in order to estimate the degree of fluctuation as a potential cause of intermittent adverse effects.

The concept of 'reference range'

Inconsistent use of terminology has created confusion in the therapeutic drug monitoring literature. Terms such as 'reference range', 'therapeutic range', 'optimal range', 'effective range', and 'target range' have all been used, either interchangeably or with different meanings.

The ILAE position paper recommends that the term 'reference range' be used to define 'a range of drug concentration which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur' [60]. Indeed, research in therapeutic drug monitoring has been aimed mostly at identifying a reference range which laboratories can quote and which clinicians can use as a guide. Although 'references ranges' of drug concentrations have been described for many antiepileptic drugs (Table 9.5), it would be incorrect to suggest that all patients should have their dosage adjusted in order to produce plasma concentrations within the indicated limits. These ranges are simply representative of the plasma concentrations at which most patients respond. There may be a large variation in the degree of response at any given plasma drug concentration, and many patients achieve control at concentrations which are below or above the reference ranges quoted in the literature. In other words, the 'reference range' is not necessarily a 'therapeutic range'. As explained in greater detail in the section below, the term 'therapeutic range' should be reserved to define 'the range of drug concentrations which are associated with the best achievable response in a given person, and therefore it can only be determined for the individual' [59]. If known, the 'therapeutic range' is clinically more useful than the 'reference

Table 9.5 Reference ranges of plasma concentrations for commonly used antiepileptic drugs.

Drug	Optimal range	Comments
Benzodiazepines	Not applicable	Plasma drug level monitoring not indicated. No consistent relationship between plasma drug concentration and effect
Carbamazepine	4–12 μg/ml (17–51 μmol/l)	Plasma drug level monitoring useful, though often dosage can be adjusted solely on the basis of clinical response
Ethosuximide	40–100 μg/ml (283–708 μmol/l)	Plasma drug level monitoring useful, though often dosage can be adjusted solely on the basis of clinical response
Felbamate	30–60 μg/ml (116–252 μmol/l)	Dosage adjustments are usually based solely on clinical response
Gabapentin	2–20 μg/ml (12–117 μmol/l)	Dosage adjustments are usually based solely on clinical response. Interpretation of plasma drug levels is complicated by marked fluctuations in drug concentrations during a dosing interval
Lamotrigine	2.5–15 μg/ml (10–58 μmol/l)	Plasma drug level monitoring is useful because dosage requirements are markedly affected by intra- and inter-individual pharmacokinetic variability
Levetiracetam	12–46 μg/ml (70–270 μmol/l)	Dosage adjustments are usually based solely on clinical response. Interpretation of plasma drug levels is complicated by marked fluctuations in drug concentrations during a dosing interval
Oxcarbazepine	3–35 μg/ml (12–139 μmol/l)	Reference range refers to the active metabolite monohydroxycarbazepine. Therapeutic drug monitoring may be useful due to significant pharmacokinetic variability
Phenobarbital	10–40 μg/ml (43–172 μmol/l)	Imprecise upper limit due to tolerance to the sedative effects
Phenytoin	10–20 μg/ml (40–80 μmol/l)	Plasma drug level monitoring very useful because of saturation kinetics and narrow therapeutic index
Pregabalin	Insufficient data	Reference range not established. Interpretation of plasma pregabalin levels is complicated by marked fluctuations in drug concentrations during a dosing interval
Primidone	4–12 μg/ml (18–55 μmol/l)	Plasma drug level monitoring of unchanged primidone seldom required. It is more relevant to measure the levels of the metabolite phenobarbital
Rufinamide	Insufficient data	Plasma drug level monitoring expected to be useful because of pharmacokinetic variability related to dose-dependent bioavailability
Tiagabine	0.02–0.2 μg/ml (0.5–5 μmol/l)	Dosage adjustments are usually based solely on clinical response. Measurement of the low concentrations of tiagabine is technically difficult and interpretation of plasma levels is complicated by marked fluctuations in drug concentrations during a dosing interval
Topiramate	5–20 μg/ml (15–59 μmol/l)	Dosage adjustments may be based solely on clinical response
Valproic acid	50–100 μg/ml (346–693 μmol/l)	Usefulness of plasma drug level monitoring limited in most cases
Vigabatrin	Not applicable	Plasma drug level monitoring not indicated, except as a check for compliance. Due to irreversible mode of action, time-course of effect is dissociated from time-course of plasma vigabatrin levels
Zonisamide	10–40 μg/ml (47–188 μmol/l)	Dosage adjustments may be based solely on clinical response

For further information and bibliography, see ref. 60.

range'; for example, if a patient is known to have become seizure free at concentrations below the lower limits of the 'reference range', those concentrations can be regarded as 'therapeutic' for that patient, and there will be no need to increase dosage.

Despite the limitations related to inter-patient variability in concentration–response relationships, 'reference ranges' are clinically useful because they provide a measure of the amount of drug which is present in the circulation and of the probability that the patient is benefiting optimally from the treatment. For example, a drug concentration below the reference range in an individual with uncontrolled seizures will give the clinician greater confidence in increasing dosage, and may help in deciding the magnitude of the dosage increment. Based on knowledge of concentration–response relationships in specific seizure types, physicians may also elect to aim initially at a predefined target drug concentration, rather than at a target maintenance dosage. Decisions must also take into consideration the patient's attitudes; for example, if an individual is likely to be very distressed by occurrence of another seizure, it would make sense to aim initially at a serum drug concentration in the upper portion of the 'reference range'. Conversely, lower concentrations may be targeted whenever tolerability concerns outweigh concerns of seizure recurrence. More examples of the use of therapeutic drug monitoring in clinical management are given in the section 'When should drug concentrations be measured?'.

The use of drug concentrations as an aid to dose adjustments does not exempt the clinician from monitoring clinical response carefully. In fact, achieving a desired drug concentration is no guarantee that an optimal response will be obtained, and many subjects experience therapeutic or toxic effects at concentrations higher or lower than expected.

Why do individuals respond differently to the same drug concentration?

Several factors are responsible for the differences in clinical response at any plasma drug concentration, and many of these are not understood completely. One major source of variability is the variation in pathophysiology of epilepsy. Because the epilepsies are a variety of disorders, heterogeneous in terms of aetiology, underlying mechanisms, type and extent and location of structural abnormalities (if present) and clinical manifestations, it is no surprise that the type and severity of epilepsy greatly affect the response to any given drug concentration. Patients with easily manageable forms of epilepsy tend to be controlled at plasma drug concentrations near or below the lower limit of the 'reference range', whereas patients with epilepsies more difficult to control (e.g. symptomatic partial epilepsies) tend to require higher levels. In a representative study, Schmidt and Haenel [40] assessed the plasma concentration required to achieve optimal seizure control in patients with different seizure types treated with monotherapy. Among 40 well-controlled patients with generalized tonic–clonic seizures, 26 achieved freedom from seizures at plasma drug concentrations below the mid-portion of the 'reference range'. Conversely, among 19 well-controlled patients with both generalized tonic–clonic and complex partial seizures, only three were controlled at plasma drug levels in the lower range. The median number of seizures during the first year of epilepsy was five for the patients who were controlled at lower concentrations compared with 29 for those who required higher concentrations. The fact that for some drugs the 'reference ranges' quoted in Table 9.5 were established mostly in relatively severe forms of epilepsy provides an explanation for the observation that in newly diagnosed patients optimal responses are not infrequently seen at concentrations lower than these. This is an important point, often overlooked by non-specialists. Because of this, it has been suggested that the lower limits of the commonly quoted 'reference ranges' should be disregarded, and that any concentration up to the upper limits of these ranges should be considered as potentially therapeutic [77].

Response at any given drug concentration may vary over time within the same individual. For example, for some drugs, therapeutic and/or toxic effects often decrease over time, due to 'adaptation' mechanisms at the site of action, despite persistence of stable drug concentrations in blood. This phenomenon, known as pharmacodynamic tolerance, is seen most frequently with benzodiazepines and barbiturates. Because of the development of tolerance to the sedative effects of these drugs, patients treated chronically with benzodiazepines or barbiturates may tolerate well plasma drug concentrations which would be very toxic and even cause coma in acutely exposed subjects [77]. With phenobarbital, tolerance to sedative effects usually does not entail a simultaneous loss of anticonvulsant activity. This is not always the case for benzodiazepines, whose therapeutic value during chronic treatment is often limited by full or partial loss of efficacy.

Apart from the heterogeneity of seizure disorders and adaptive changes at the site of drug action, other factors contribute to variability in the relationship between plasma drug concentration and response. These include alterations in the degree of drug binding to plasma proteins (see the section below on monitoring unbound drug concentrations) and the confounding effects of active metabolites and pharmacodynamic interactions with concomitant medications. Plasma concentrations of the active metabolites of some antiepileptic drugs are not routinely measured, and therapeutic errors may arise when the concentrations of the parent drug are interpreted without taking into account the potential contribution of metabolites [60]. For example, addition of valpromide, a valproic acid derivative, to the regimen of patients stabilized on carbamazepine causes a marked increase in the plasma concentration of the active metabolite carbamazepine-10,11-epoxide [78], resulting frequently in signs of intoxication (Fig. 9.1). Since the plasma concentration of the parent drug is not affected by this interaction, monitoring plasma carbamazepine concentration provides no clue to the mechanism underlying the development of adverse effects. A similar situation arises in the presence of drugs which interact at pharmacodynamic levels. Since the adverse central nervous system effects of antiepileptic drugs may be additive, it is not uncommon for patients on multiple drug therapy to develop clinical signs of toxicity at drug concentrations within or even below the 'reference ranges' quoted in the literature [4].

The concept of individual 'therapeutic concentrations'

The marked interindividual variability in response at any drug concentration complicates the interpretation of therapeutic drug

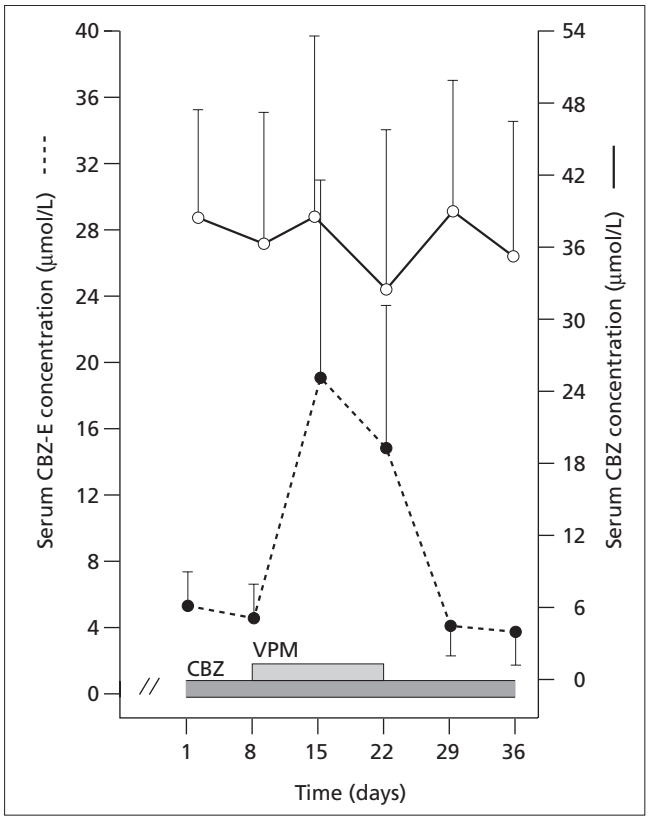

Fig. 9.1 Effect of valpromide (VPM, 1200 mg/day for 2 weeks), the amide derivative of valproic acid, on the serum concentration of carbamazepine (CBZ) and its active 10,11-epoxide metabolite (CBZ-E) in six patients stabilized on a constant dosage of carbamazepine. Values are means ± SEM. Note the marked elevation in the concentration of carbamazepine-10,11-epoxide after addition of valpromide, an inhibitor of the enzyme responsible for the conversion of the epoxide to the corresponding diol. The apparent decrease in the concentration of carbamazepine-10,11-epoxide on day 14 of combined therapy (compared with day 7) is due to exclusion of two patients with very high concentrations of the metabolite, who required discontinuation of valpromide because of side-effects. Data from ref. 78.

monitoring data. However, the fact that the optimal concentration of an antiepileptic drug varies from patient to patient does not eliminate the value of therapeutic drug monitoring. In fact, in clinical practice it is often possible, and even desirable, to establish empirically the plasma concentration at which an individual patient exhibits the best response [60,79]. In other words, once dose has been adjusted on the basis of clinical response and an optimal effect has been achieved, the concentration associated with such an outcome can be measured and considered as an estimate of the 'therapeutic concentration' in that individual. Depending on the characteristics of the individual, an optimal response may be either sustained seizure freedom, or the best compromise between reduction in seizure frequency and adverse effects. Establishing an individual 'therapeutic concentration' (or 'therapeutic range', if repeated concentration measurements are taken in a patient who achieved an optimal response) may require considerable time, particularly in seizure-free patients in whom prolonged observation may be needed to confirm that sustained remission has been obtained.

The 'therapeutic concentration' in an individual, once established, provides useful information for subsequent management. For example, if a few years later the same individual will experience a seizure breakthrough, a second measurement of the plasma drug concentration may provide clues as to the possible causes [80]. In particular, if at the time of the seizure breakthrough the drug concentration is found to be lower than the previously established 'therapeutic concentration', there is a strong indication that the relapse was due, depending on clinical context, to either a change in compliance or a change in drug disposition under the influence of physiological factors, disease states or drug interactions [60]. Knowledge of the plasma concentration at which that individual had responded in the past will also aid in deciding what dosage adjustments will be needed if seizure breakthrough was caused by altered drug disposition.

Whenever a patient is exposed to conditions known or suspected to alter plasma drug levels, information on the 'therapeutic concentration' in that individual may be used to prevent recurrence of seizures or drug toxicity. For example, oral contraceptives are known to cause a marked but variable decrease in plasma lamotrigine concentration [15]. If the individual 'therapeutic concentration' of lamotrigine is known in a woman with well-controlled epilepsy who is starting an oral contraceptive, serial drug level monitoring will enable rapid detection of contraceptive-induced changes in lamotrigine concentration, and appropriate dose adjustments can then be made to restore the 'therapeutic concentration' of the drug and thereby prevent possible seizure recurrence. Another example of the application of the 'therapeutic concentration' concept can be found in a recent study on the consequences of a fall in plasma lamotrigine levels during pregnancy [81].

The determination of individual 'therapeutic concentrations' is a useful tool which can be applied to any antiepileptic drug, including new-generation drugs [79]. To ensure optimum accuracy in establishing 'therapeutic concentrations', sampling time must be standardized carefully, and at least two determinations should be obtained on different dates, in order to assess the variability of the estimate. It is also important to remember that even carefully determined 'therapeutic concentrations' need to be interpreted flexibly, because the patient's sensitivity to a given drug concentration may change over time. This may occur as a result of alterations in the pathophysiology of the seizure disorder (particularly during the period of brain maturation), pharmacodynamic interactions with concomitant medications, or changes in drug binding to plasma proteins due to disease or displacement by interacting drugs [60,79].

Value of therapeutic drug monitoring of individual drugs

The value of therapeutic drug monitoring is greatest for phenytoin, for which the relationship between plasma concentration and effect is relatively consistent (Table 9.5). Since the enzymes responsible for phenytoin metabolism become saturated at clinically occurring concentrations, small changes in phenytoin dosage can produce disproportionately large changes in drug concentration. Under these conditions, knowledge of the plasma concentration is particularly important in deciding the magnitude of dosage adjustments; in particular, when the steady-state phenytoin

concentration approaches the lower limit of the 'reference range', dose increments should be very small to minimize the risk of intoxication [56,60].

A relatively good relationship between plasma concentration and response is also observed with ethosuximide and carbamazepine, but the dosage of these drugs can be individualized relatively easily on the basis of clinical response [77]. In the case of phenobarbital, interpretation of plasma drug concentrations is complicated by the development of tolerance, which causes a large variation in the levels at which toxicity occurs. For valproic acid, the relationship between concentration and response is rather variable, but some adverse effects, such as tremor, certain encephalopathic symptoms and changes in platelet function, may be related to high plasma valproic acid concentrations, and monitoring valproic acid levels may be of particular value when toxicity is suspected or in patients receiving high dosages [77].

Among second-generation antiepileptic drugs, therapeutic drug monitoring is particularly useful for lamotrigine, the plasma concentrations of which exhibit large inter- and intra-individual variability under the influence of age, pregnancy and drug interactions [60]. Topiramate, zonisamide, oxcarbazepine, gabapentin, rufinamide, levetiracetam, pregabalin, tiagabine and felbamate also show marked pharmacokinetic variability, which is likely to contribute to differences in dosage requirements. The concept of 'individual therapeutic drug concentration' may be of special value in optimizing monitoring of some of these medications. For short-half-life drugs such as levetiracetam, gabapentin, pregabalin and tiagabine, interpretation of drug monitoring data is complicated by the variability caused by prominent fluctuations in drug levels during a dosing interval.

Monitoring unbound drug concentrations

Although routine analytical methods measure the total concentration of the drug in plasma, it is only the free, non-protein-bound fraction which is available to equilibrate with receptor sites and to produce pharmacological effects. When the unbound fraction is increased, the total concentration in plasma may underestimate the amount of drug which is pharmacologically active, and this should be taken into account when interpreting the plasma concentration of highly protein-bound drugs such as phenytoin and valproic acid [60]. An increased unbound fraction of these drugs is observed in conditions associated with hypoalbuminaemia (e.g. neonatal age, advanced pregnancy, old age, chronic liver disease, nephrotic syndrome) or accumulation of endogenous displacing agents (e.g. uraemia). An increase in unbound fraction may also be caused by drug interactions: valproic acid, for example, increases the unbound fraction of phenytoin by displacing phenytoin from protein binding sites. In all these conditions, therapeutic and toxic effects may be observed at total drug concentrations lower than usual, and failure to recognize this may mislead the clinician into making inappropriate dosage adjustments. The suggestion has been made that in the presence of altered binding to plasma proteins it would be preferable to monitor directly the unbound drug concentration. In practice, however, this is not always necessary because often the increase in unbound fraction may be predicted on the basis of other parameters such as plasma albumin or, in uraemic patients, plasma creatinine concentration. In addition, unbound plasma drug concentrations are much smaller than total concentrations and not always easy to measure. Results may vary depending on the assay technique, and there is a greater possibility of analytical error than with measurements of total drug concentrations.

With certain drugs such as carbamazepine and phenytoin, the concentration in saliva correlates relatively well with the unbound concentration in plasma [60]. Therefore, salivary concentrations have been proposed for monitoring purposes, particularly in children who find venepunctures distressing. However, the use of salivary samples is not without problems because leakage of exudate (e.g. due to gingivitis) or dose residuals in the mouth may lead to erroneous results. Moreover, as mentioned above, measuring drug concentrations is subject to error, particularly when laboratories do not apply rigorous quality control measures, and such errors are more likely to occur with salivary samples, partly due to the fact that for some drugs the concentration in saliva is much lower than in plasma. Furthermore, it should be stressed that the relationship between unbound drug concentration in plasma and drug concentration in saliva is not the same for all drugs [60]. In the case of phenobarbital, the concentration in saliva is dependent upon salivary pH and cannot be used as a measure of free concentration in plasma unless calculations are made to account for differences in pH. For valproic acid, measuring salivary concentrations is meaningless because the drug concentration in saliva bears no consistent relationship with the concentration in plasma.

When should drug concentrations be measured?

The practice of monitoring plasma drug concentrations, introduced in the 1960s, has played a major role in improving the quality of epilepsy care. It is thanks to therapeutic drug monitoring that many drug interactions have been discovered, and plasma drug level measurements have contributed greatly to stimulating awareness about the need to tailor dosage to the individual patient [60]. As a result of these advances in knowledge, however, physicians have also acquired skills in utilizing antiepileptic drugs correctly even without the aid of plasma drug concentrations. Antiepileptic drug therapy can be optimized on purely clinical grounds, as shown in a trial where no differences in outcome were observed between patients randomized to have their dosage adjusted empirically and those in whom dosage was tailored based on drug concentration measurements [82]. It should be noted, however, that few patients in that trial were treated with phenytoin, the drug for which measurement of plasma concentrations is particularly useful.

If the concept of individualized 'therapeutic drug concentrations' is accepted, a case can be made for determining plasma drug concentrations in any patient who has been stabilized on a satisfactory drug regimen. As discussed in some detail above, the information derived from these measurements can be extremely useful for subsequent management, particularly when a patient shows an unexpected change in clinical response or is exposed to conditions causing pharmacokinetic changes.

In routine clinical practice, there are many other situations in which measuring plasma drug levels may be indicated [60]:

- At the onset of treatment, if the physician elects to stabilize the patient on a desired target concentration, rather than a desired target maintenance dosage.
- When the patient fails to achieve an adequate therapeutic response despite an apparently adequate dosage. In this situation, assessment of the drug concentration will be useful in identifying potential sources of poor response, such as low drug concentrations due to unusual pharmacokinetic patterns or poor compliance.
- In the presence of physiological or pathological conditions known to be associated with pharmacokinetic changes. These include paediatric age, pregnancy, old age and diseases affecting the liver, the kidney and the gastrointestinal tract. If applicable, knowledge of a pre-established individual 'therapeutic concentration' is of particular value in the management of these patients. However, it should be noted that, in some of these conditions, drug binding to plasma proteins and pharmacodynamic sensitivity to the drug may also be altered, and this should be taken into account when interpreting concentration data. For example, if an emergent condition resulted in an increased unbound fraction of the drug, therapeutic and toxic effects will be expected to occur at comparatively lower total drug concentrations.
- In establishing a differential diagnosis of drug toxicity. This is especially important when toxic symptoms (e.g. exacerbation of seizure frequency, incoordination or mental symptoms) may not be differentiated easily from those of underlying or associated diseases, or when the patient is unable to report adverse effects properly (young children or unconscious patients).
- To minimize the difficulties in dosage adjustments caused by dose-dependent pharmacokinetics, particularly with phenytoin.
- In patients receiving multiple drug therapy, in order to identify and to minimize the consequences of adverse drug interactions. When seizure control is unsatisfactory or toxic signs develop in patients on polytherapy, measuring the concentration of individual drugs (or their active metabolites, for instance carbamazepine-10,11-epoxide) may also assist in identifying the agent whose dosage should be preferentially adjusted.
- When a drug formulation has been changed, to assess the possibility of a clinically significant change in bioavailability.
- When poor compliance is suspected. Compliance problems are suggested by unusually low and variable concentrations, which increase following supervision of drug intake.

Use of therapeutic drug monitoring requires a close collaboration between clinicians and their laboratory colleagues. Adequate quality control measures must be in place to ensure the reliability of the analytical determinations, and apparent discrepancies between the patient's status and therapeutic drug monitoring results should be appropriately evaluated and discussed.

While the value of therapeutic drug monitoring cannot be questioned, it should be recognized that drug concentrations are often measured unnecessarily or interpreted incorrectly [76]. These determinations should be requested only when there is a sound indication, and dosage adjustments should be made only when there is a clinical need, irrespective of the drug level in the blood. Physicians must always remember that the primary aim of therapy is to treat a patient and not a laboratory value.

How long should treatment be continued?

Since many epilepsies are prone to undergo spontaneous remission, the possibility of discontinuing antiepileptic medication after an adequate period of seizure freedom should be considered. This is especially important in children, who show a higher prevalence of self-remitting syndromes and in whom the psychosocial consequences of seizure relapse are less severe than in adults. The option of discontinuing treatment should be discussed with the patient and the family, taking into consideration not only the probability of relapse, but also any adverse effects of treatment, the patient's attitude to continuation of treatment and to the possibility of seizure recurrence, and legal implications with special reference to driving regulations.

Because stopping antiepileptic drugs abruptly may cause withdrawal seizures and even status epilepticus, discontinuation of medications should be carried out gradually, to allow assessment of response at each dose level and to minimize risks. The proportion of patients whose seizures recur within 2 years following discontinuation of therapy is on average about 30% [83], but this figure in itself has limited meaning in individual cases because relapse rates range from close to zero to over 90% depending on the characteristics of the population. Predictors associated with an increased risk of relapse include increasing age, partial seizures, symptomatic epilepsy, an abnormal EEG and a longer duration of active disease prior to seizure control. Another important prognostic factor is the epilepsy syndrome, with relapse rates being lowest in rolandic epilepsy and highest in juvenile myoclonic epilepsy [84].

Generally speaking, stopping medication always carries some risk of recurrence, and a decision about drug withdrawal should be based on an assessment of the benefits versus risks. This is an individual and sometimes difficult decision, which should be taken by the patient after full appraisal of the relevant facts. A detailed discussion of clinical management of patients in remission is given in Chapter 12.

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10 Management of Newly Diagnosed Epilepsy

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The implications of newly diagnosed epilepsy

The diagnosis of epilepsy has important medical and social implications. The seizures themselves may cause injury and embarrassment, as well as anxiety about the underlying cause (particularly brain tumour). The secondary effects of seizures are likely to affect many aspects of everyday life. Loss of the driving licence is often particularly distressing, causing loss of independence, with consequences for employment, finance and even housing if a mortgage is involved or the patient lives in an isolated area. Leisure activities are likely to be affected and, for children, epilepsy may disrupt education. Medication may cause adverse effects and concerns about teratogenicity and breastfeeding for women with epilepsy. Finally, parents often worry that their children will inherit the epileptic tendency. For all these reasons, it is essential both to ensure that the diagnosis is correct before considering treatment and to provide the patient with adequate education and information about the condition.

The diagnosis of epilepsy

Epilepsy has been defined as 'the tendency to recurrent unprovoked seizures'. Diagnosis involves not only confirmation of the fact that the person is having seizures, but also classification of the seizure type, which guides the choice of antiepileptic treatment, and the epilepsy syndrome, with its implications for long-term prognosis. The International Classification of Epileptic Seizures and International Classification of Epilepsies and Epileptic Syndromes produced by the International League against Epilepsy [1,2] are commonly used for this purpose. An attempt should also be made to identify the underlying cause.

The differential diagnosis of epilepsy is wide (Table 10.1), with syncope and psychogenic non-epileptic seizures being the most frequently encountered (see Chapter 4). Except in the rare situation in which the patient has a seizure while undergoing recording of an electroencephalogram (EEG), the diagnosis of epilepsy is made on the basis of the clinical history, taken both from the patient and from someone who has observed the seizures. It may be impossible to make the diagnosis with certainty in the absence of an eye-witness description, particularly where the seizure involves loss of consciousness. In addition to the description of the attack, information should be sought regarding the presence or absence of precipitating factors, duration and severity of postictal phase, family history of epilepsy, other medical history indicating a possible predisposition towards seizures or other paroxysmal conditions (for example, prolonged febrile seizure, head injury, somatization disorder), drug history and alcohol intake. Diagnosis may be difficult, and in one study [3] it was found that up to 20% of patients admitted to a psychiatric hospital with refractory epilepsy did not have this disorder.

The routine EEG is of low sensitivity in making the diagnosis of epilepsy. Only about 35% of patients with epilepsy consistently show epileptic abnormalities on their EEG [4], although the yield is increased by repeated recordings, particularly with sleep deprivation [5]. In patients presenting with a suspected single seizure, the proportion with epileptic abnormalities may be as low as 21% [6]. However, only 0.5% of people without seizures show epileptic abnormalities in their EEG, which may thus be helpful in confirming a diagnosis of epilepsy in those with a suggestive history [7]. The EEG may be useful in determining whether seizures are generalized or partial.

The epilepsy syndrome has implications for both prognosis and treatment. For example, benign epilepsy of childhood with centrotemporal spikes usually remits by puberty, while juvenile myoclonic epilepsy is associated with a very high risk of relapse without medication [8]. However, it may be difficult to identify the epilepsy syndrome at the time of presentation. King *et al.* [9] studied 300 consecutive adults and children over the age of 5 years presenting with unexplained seizures. Although the intention was to study patients presenting with a first generalized tonic–clonic seizure, 17% were found to have had previous similar events and 28% had experienced other epileptic symptoms, such as absences, myoclonus or temporal lobe auras. An EEG was performed within 24 h of the seizure where possible, and magnetic resonance imaging (MRI) scanning was also performed electively. The authors could diagnose a generalized or partial epilepsy syndrome clinically in 141 patients (47%), with only three of these clinical diagnoses later being proved incorrect: after EEG and MRI, it was possible to diagnose 81% of patients as having a generalized epilepsy (23%) or partial epilepsy (58%). Jallon *et al.* [10] studied 1942 patients presenting with unprovoked seizures, of whom 47.7% had had a single seizure and 52.3% more than one seizure at initial presentation, most of whom underwent EEG and neuroimaging. In the group presenting after a single seizure, 46.2% had partial seizures, 31.9% generalized seizures and 21.9% unclassified seizures. Among those having more than one seizure by the time of presentation, the first seizure type was partial in 48.1%, generalized in 39.9%

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and unclassified in 12%. An epilepsy syndrome could be assigned in 98.6% of patients having more than one seizure at the time of diagnosis.

Rationale for treatment

As indicated above, the diagnosis of epilepsy has important medical and social implications. The decision whether to start medication depends on the likelihood of recurrence and an evaluation of the risk of harmful consequences from the seizures themselves (including injury, death, psychosocial morbidity and the effect of recurrent seizures on long-term prognosis) weighed against the adverse effects of medication.

Risk of recurrence after a first seizure

Estimates of the risk of recurrence following a first seizure have varied widely from 27% by 3 years [11] to 84% after a variable period of follow-up [12]. The true figure probably lies somewhere in between. In the FIRST seizure study of patients seen within 1 week of their first generalized tonic–clonic seizure [13], the risk of recurrence in untreated patients was 51% by 1 year. In the MESS study [14] of immediate versus deferred antiepileptic drug (AED) treatment for early epilepsy and single seizures, Marson *et al.* found a recurrence rate in untreated patients at 2 years of 39% in those patients randomized after a single seizure, and 61% in those having multiple seizures before randomization.

The differences between the various studies can largely be explained on the basis of variations in study design. The time elapsing between the time of first seizure and entry into the study is particularly important, since the risk of recurrence is greatest in the first few weeks after the first seizure [15] (Fig. 10.1), and any delay in recruiting the patient to the study will exclude those who have already had a second seizure, leading to an artificially low recurrence rate. A further problem in assessing recurrence is the difficulty in making the diagnosis at the outset, particularly if the initial seizure is unwitnessed, or if earlier seizures have been mild (for example, absences, myoclonus or simple partial seizures), a fact illustrated by the Rochester study of Hauser *et al.* [16], which found that the time from the first afebrile seizure to diagnosis was longer than 6 months in 50% of patients, and longer than 2 years in more than 30%. The use of crude recurrence rates may also lead to distortion through incomplete follow-up, as may bias where the study design is retrospective.

The influence of aetiology, seizure type, age of the patient, EEG abnormalities, timing of first seizure (during sleep or while awake) and coexistence of mental retardation or other neurological abnormalities on risk of recurrence is controversial. The First Seizure Trial Group [13] found a 1.7-fold increase in the risk of recurrent seizures in patients with epileptiform abnormalities on their EEG. This study also found age less than 16 years and remote aetiological factors to be predictive of relapse, whereas acute treatment of the initial seizure with benzodiazepines was associated with a lower subsequent relapse rate [17]. Van Donselaar *et al.* [18] similarly found the presence of epileptic discharges on EEG to be strongly predictive of seizure recurrence. Other factors increasing the risk of recurrence in this study were younger age, occurrence of first seizure during sleep or on awakening, and tongue biting. Hauser *et al.* [11] also found the EEG to be helpful in predicting prognosis among patients with idiopathic seizures, those with a generalized spike–wave pattern having a significantly higher rate of recurrence (50% at 24 months, compared with 14% in those with normal or non-specific tracings). However, risk of recurrence was not significantly increased by focal slowing or spikes compared with normal or non-specifically abnormal tracings. Other adverse factors in this study included a known remote aetiology for a first seizure, Todd's paresis following the first seizure, and a history of acute symptomatic seizures. The MESS study found

Table 10.1 Conditions that may be confused with seizures.

Vasovagal syncope
Cardiac dysrhythmias
Non-epileptic seizures (of psychological origin)
Panic attacks
Migraine
Breath-holding attacks (in children)
Sleep terrors and other parasomnias
Other paroxysmal movement disorders (e.g. paroxysmal kinesigenic choreoathetosis)
Narcolepsy/cataplexy
Vertigo
Hypoglycaemia
Other metabolic disorders
Alcohol/substance abuse

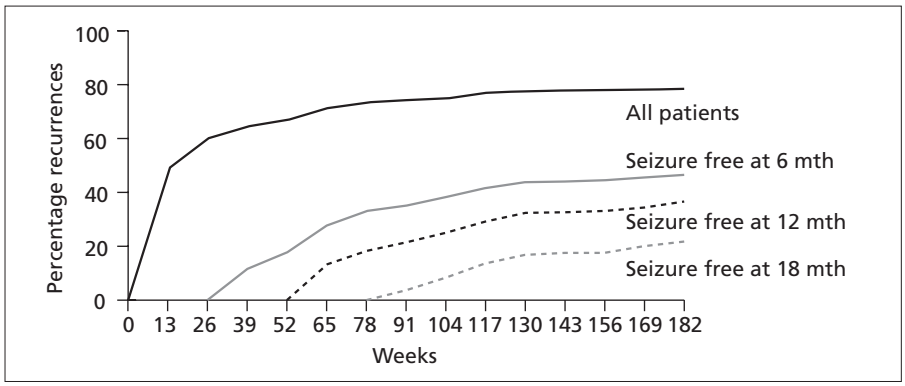

Fig. 10.1 National General Practice Study of Epilepsy: actuarial percentage of recurrence after first seizure. A study of 564 patients followed prospectively from the time of diagnosis. Within 3 years of their first seizure, 78% of patients had a recurrence of their attacks. If attacks had not recurred within 6, 12 or 18 months, the chance of recurrence was substantially reduced, falling to 44%, 32% and 17%, respectively. From ref. 15.

number of seizures of all types at presentation, presence of a neurological abnormality, and an abnormal EEG, to be significant factors in predicting future seizures [19].

Seizure aetiology was of prognostic importance in the National General Practice Study of Epilepsy [15]. Recurrence was lower in patients experiencing acute symptomatic seizures (seizures occurring in the context of an acute insult to the brain, such as stroke, head injury or encephalitis, or as a result of drugs or metabolic disturbance) than in those with idiopathic seizures or seizures due to a remote symptomatic cause. Seizures associated with a neurological deficit presumed present at birth had the highest rate of recurrence (100% by 18 months). Other factors associated with an increased risk of recurrence were age (the highest risk being for patients under the age of 16 or over the age of 59) and seizure type, recurrence being higher in patients with simple or complex partial seizures.

A meta-analysis of 16 studies examining the risk of recurrence after a first seizure was carried out by Berg and Shinnar [20], who concluded that seizure aetiology and the EEG were the strongest predictors of recurrence.

Effect of repeated seizures on risk of recurrence

Several studies suggest that the risk of recurrence is increased in patients who have a second or third seizure. Hauser *et al.* [21] studied 204 patients with a first unprovoked seizure prospectively for 5 years or until the time of the third seizure. The overall recurrence rate was lower than in many other studies, only 33% (95% CI 26–40%) having a second unprovoked seizure within 5 years of the first. Among the 63 patients who had a second seizure, the risk of further unprovoked seizures was 32% by 3 months, and 73% by 4 years. Of note in this study is that 432 patients were excluded through having had multiple seizures before their first medical evaluation, emphasizing the late presentation of many patients with epilepsy: similarly in the National General Practice Study of Epilepsy [15] only 44.7% of patients were registered at the time of their first seizure, and in the CAROLE study (Coordination Active du Réseau Observatoire Longitudinal de l'Epilepsie [10]) 52.3% of patients had already had two or more seizures at the time of presentation. In line with these studies are the observations of MacDonald *et al.* [22], who carried out a population-based study following patients newly presenting with seizures prospectively, and found that the number of seizures in the 6 months following presentation was the single most important predictive factor for both early and long-term remission of seizures.

Effect of treatment after a first seizure on risk of recurrence

In a number of studies, assessment of recurrence rate has been confounded by the fact that some patients are treated following their first seizure. Usually this is not random, with treatment being started in those patients who are considered to be at higher risk of recurrence, and, because of this, such patients are usually retained within the study to avoid bias. The effect of medication on recurrence as determined in these studies has been confusing: in the National General Practice Study of Epilepsy [15] patients starting medication after a first seizure had a lower risk of recurrence [50% (95% CI 40–61%) by 1 year], whereas other trials [11,23] have found no difference in the risk of recurrence between treated and untreated patients.

In four studies in which patients have been randomized to immediate or delayed treatment following a single seizure, however, a clear reduction in the risk of seizure recurrence has been shown. The largest such study was carried out by the MESS Study Group [14]. Overall 722 patients with early epilepsy or single seizures were assigned to immediate treatment with AEDs, and 721 to deferred treatment. The recurrence rate at 2 years was 32% for those assigned immediate treatment following a single seizure compared with 39% for those whose treatment was deferred (difference 11%, 95% CI 6.2–16.7), and 43% for those assigned immediate treatment following multiple seizures at randomization compared with 61% for those assigned deferred treatment.

The First Seizure Trial Group [13] was a multicentre study of 397 patients aged from 2 to 70 years presenting within 7 days of a first generalized tonic–clonic seizure (excluding acute symptomatic seizures and seizures associated with progressive neurological disorders, metabolic disorders or alcohol) and randomized to immediate treatment with carbamazepine, phenytoin, phenobarbital or sodium valproate, according to the preference of the physician. Analysis was on an intention to treat basis. Among the treated group, the probability of recurrence was 4% by 1 month, 7% by 3 months, 9% by 6 months, 17% by 1 year and 25% by 2 years: the corresponding figures for the untreated subjects were 8%, 18%, 41% and 45%. The hazard ratio of relapse for untreated subjects, estimated by the Cox proportional hazard model adjusting simultaneously for the prognostic predictors, was 2.8% (95% CI 1.9–4.2). The effect of treatment was even greater in those compliant with medication: among the 20% allocated to treatment who discontinued it at some time, 27% had a relapse, compared with only 15% in whom compliance was good. However, even among the group not receiving treatment, fewer than 50% had a recurrence within 2 years. A similar difference in recurrence rate was noted in two smaller studies [24,25].

Effect of treatment on long-term prognosis

There has been considerable debate about the effect of treatment on the long-term prognosis of epilepsy [26–28]. Gowers' view was that the occurrence of seizures facilitated the development of further seizures. This standpoint has been endorsed by Reynolds [29], who noted that among patients with newly diagnosed epilepsy treated with AEDs, the most important influence on prognosis was the number of seizures prior to starting treatment, along with a declining interval between seizures in patients with new epilepsy [30], suggesting an accelerating process in the development of epilepsy.

Others have argued that the hypothesis that early AED treatment improves the prognosis of epilepsy has not been proven. Chadwick [28] pointed out that the prognosis for certain epilepsy syndromes is consistent regardless of treatment. Hence benign epilepsy of childhood with centrotemporal spikes almost invariably remits by puberty, while the prognosis for relapse in juvenile myoclonic epilepsy is consistently high after withdrawal of treatment. O'Donoghue and Sander [31] noted the importance of other factors, such as aetiology, on prognosis, with remission rates for those with neurological deficits present since birth being

considerably poorer than those seen in idiopathic or cryptogenic epilepsy.

Several studies have suggested that the latter view may be correct. The FIRST Seizure Trial Group [17] found no significant difference in longer-term outcome between patients randomized to treatment after a first unprovoked seizure and those in whom treatment was delayed, although early recurrences were more common in the latter group. The MESS study similarly found that immediate antiepileptic drug treatment did not affect long-term remission in individuals with single or infrequent seizures [14]. Indirect evidence is provided by a study by Feksi *et al.* [32] of 302 patients with active seizures randomized to treatment with carbamazepine or phenobarbital in rural and semi-urban Kenya. Fifty-three per cent of patients became seizure free in the second 6 months of therapy (the two drugs being equally effective) and a further 26% had a reduction in their seizures of greater than 50% compared with their pretreatment frequency. The effect of therapy was not influenced by the duration of epilepsy (more or less than 5 years) prior to treatment or by the lifetime number of seizures before treatment.

Two surveys of people with epilepsy who remained untreated also indicate that epilepsy may run a benign course in many people. In a community-based survey undertaken in Ecuador [33], 44% of all patients who were identified as having had epilepsy had been free of seizures for at least 12 months, even though nearly two-thirds of these had never received treatment with antiepileptic drugs. Similarly, in a survey of all people living in the Kuopio University Hospital district in Finland who had had at least two unprovoked non-febrile seizures, 50 patients (4.1%) had never had their seizures treated. Of 33 patients who were followed for at least 2 years, the probability of remission was 42% at 10 years and 52% at 20 years after the onset of epilepsy [34]. The balance of evidence from the available studies is thus now firmly against the view that failure to treat early results in a worse outcome.

It has been argued that seizures might cause intellectual deterioration, which could be prevented by antiepileptic drug treatment. On occasion, falls owing to seizures cause significant head injury, which can result in cognitive problems [35]. However, with respect to seizures in general, no significant deterioration was found in the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke [36], which compared a cohort of children studied from birth to the age of 7, who developed seizures between the ages of 4 and 7 years, with age- and sex-matched control subjects of the same socioeconomic level and the same IQ score at the age of 4 years. There was no significant difference in IQ from the control group at the age of 7 years. Further studies are required in this area.

Risk of mortality in early epilepsy

Until recently, little research had been carried out into sudden unexpected death in epilepsy (SUDEP) and other causes of increased mortality. Measurement of excess mortality is difficult owing to poor documentation of both epilepsy and cause of death. It is now recognized, however, that the standardized mortality ratio (SMR) in people with epilepsy is of the order of 2–3. It is higher in the first few years after diagnosis and in males, those with learning disabilities, those with symptomatic (rather than idiopathic or cryptogenic) epilepsy, those with convulsive seizures and younger age groups [37]. Causes of this excess mortality include accidental death or drowning due to seizures, death due to the underlying cause, suicide, aspiration, status epilepticus, complications of treatment and sudden unexplained death in epilepsy. The risk of the last has been estimated at between 1 in 500 and 1 in 1000 per year but is higher in those with severe epilepsy, reaching around 1 in 100 per year in those rejected for epilepsy surgery or in whom epilepsy surgery is not successful [38]. Data about death early after the onset of epilepsy are sparse. Loiseau *et al.* [39] examined the short-term mortality of epilepsy after a first epileptic seizure. Overall, 149 out of the 804 patients had died by the end of the first year of follow-up [compared with 16 expected, SMR 9.3 (95% CI 7.9–10.9)]. In nine patients death occurred during a seizure, and in a further 14 the cause of death was unknown; in this group patients died suddenly, sometimes without witnesses and without postmortem, but with a history of other disease. In total, 96 patients died of underlying disease and 30 of causes thought to be unrelated to seizures. Overall, the SMR was 0.0 for patients with idiopathic epilepsy, 1.6 (95% CI 0.4–4.1) for those with cryptogenic epilepsy and 19.8 (95% CI 14.0–27.3) for symptomatic seizures in progressive conditions. Further studies will be required to confirm the incidence of preventable death after a first seizure, which may influence the policy of waiting until a second seizure before starting treatment.

Risk of injury

Accidental injury owing to seizures is common, although studies are few and mainly retrospective. In one community-based study in which an unselected population of patients was mailed questionnaires, 24% of those having at least one seizure during the previous year had had a head injury, 16% a burn or scald, 10% a dental injury and 6% some other fracture [40]. Seizure frequency, seizure severity and sex were predictors of burns or scalds; seizure severity was a predictor of dental injury, and seizure severity and type were predictors of head injury. Another clinic-based survey of 244 patients reported that 25 had had at least one seizure-related burn requiring medical attention, all during seizures involving impairment of consciousness: 12 required hospitalization [41]. Other predictors were the lifetime total number of seizures, the presence of interictal neurological impairment and gender. Such a clinic-based study may be biased in including patients with more severe epilepsy. In a similar retrospective clinic-based survey by Neufeld *et al.* [42], 30% (91 out of 298 patients) reported trauma at some time, with 185 events in total, of which 61 were severe. However, this translated to a rate of only one seizure-related injury every 21 patient-years, with a serious injury every 64 patient-years. Head injury was the most common (55% of events). Those suffering injury had an earlier onset of epilepsy, and were more likely to have tonic–clonic seizures generalized from the onset, complex partial, myoclonic or absence seizures. The risk was less in those with secondary generalization. Even children with typical absence epilepsy are prone to injury, with 16 out of 59 patients (27%) in one study [43] having experienced an accidental injury at some time during an absence seizure (9% per person-year). Eighty-one per cent of these injuries occurred during the course of treatment. This fact, and the relatively low risk of injury per patient-year found by Neufeld

et al. [42], suggests that the risk of injury owing to seizures should play only a minor part in the decision as to when to start antiepileptic drugs.

Psychosocial morbidity

Epilepsy also causes considerable psychosocial morbidity. Patients with newly diagnosed epilepsy recruited into the National General Practice Study of Epilepsy [44] had difficulty accepting the diagnosis and feared future seizures and the effect of stigma on employment. In another study on quality of life involving more than 5000 people with epilepsy from 15 European countries, 48% worried a lot or some about their epilepsy and a similar proportion felt that it affected their plans and ambitions for the future [45]. Their feelings about themselves, and their social life, were also affected. Jacoby *et al.* [46], in a UK community-based study, found that patients with active seizures were more likely to be anxious or depressed, and to feel that their lives were significantly affected by the epilepsy: they were also less likely to be married and more likely to be unemployed or registered 'permanently sick'.

Adverse effects of drugs

Adverse effects of antiepileptic drugs affect a significant minority of patients. They range from mild to life-threatening and often adversely affect adherence to medication. They include symptoms of acute toxicity (such as the ataxia and blurred vision which occur with excess carbamazepine, phenytoin or lamotrigine); chronic toxic symptoms (for example, gingival hyperplasia occurring in about one-third of patients taking phenytoin); idiosyncratic reactions, such as skin rash; and teratogenicity.

The systems mainly affected by adverse antiepileptic drug reactions are the central nervous system, liver, skin and bone marrow [47]. The central nervous system is often affected by dose-related acute toxicity, causing sedation, lethargy and dizziness. Other adverse effects on the central nervous system include psychosis, reported with various drugs, and mood or behavioural changes, such as those seen with phenobarbital. Phenytoin, carbamazepine and phenobarbital induce the hepatic microsomal enzymes, and elevations of alkaline phosphatase and γ-glutamyltransferase, commonly seen in patients taking these drugs, are usually of no clinical significance. Occasionally severe, and sometimes fatal, hepatotoxicity occurs in association with valproate use, mainly in children under the age of 2 years receiving polytherapy [48]. Haematological abnormalities may be clinically unimportant, as is often the case with the mild leucopenia seen in 12% of people receiving carbamazepine therapy [47], but also include such life-threatening conditions as aplastic anaemia. Valproate, not infrequently, causes a dose-related thrombocytopenia, which is usually mild. Dermatological adverse effects are sometimes severe, and include Stevens–Johnson syndrome and exfoliative dermatitis.

Finally, it should be noted that antiepileptic therapy only produces complete seizure control in around 70–80% of patients. In those whose seizures are not fully controlled, antiepileptic drugs are often still beneficial, for example by reducing the severity of seizures (perhaps preventing secondary generalization), or the seizure frequency. Where seizure control is not achieved, however, it is important to minimize adverse effects by reducing the amount of medication to that required to produce the benefit. This is particularly the case where multiple drugs have been introduced and thus when the risk of toxicity is increased considerably.

When to start medication

The adverse effects mentioned above mean that certain criteria should be fulfilled before antiepileptic medication is started (Table 10.2). The diagnosis must be secure, particularly because treatment usually continues for several years. 'Trials of treatment', which rarely clarify the situation and may introduce additional complications, should be avoided. Other factors to be considered include the risk of seizure recurrence (bearing in mind the time elapsing since the last seizure), and the severity and frequency of seizures. The epilepsy syndrome is also important in determining prognosis and, as such, will affect the decision to start or withhold treatment. In the UK, it is usual not to treat after a single seizure, unless a specific factor makes recurrence more likely (for example, the presence of a cerebral tumour or of clear epileptic abnormalities in the interictal EEG). In contrast, in the USA it was, until recently, commonplace for patients to be treated after a first seizure [11], perhaps on account of driving, medicolegal issues or concern that the epilepsy might be progressive. The final decision must depend on an appreciation by the patient of all the risks and benefits of medication. The patient should also be aware of the fact that, once started, antiepileptic drugs are usually continued for at least 2 years, based on the likelihood of recurrence after withdrawal of medication, which has been shown to decrease with increasing length of time since the last seizure [49].

Wishes of the patient

Although most patients would prefer neither to have seizures nor to need medication, for some, the risk of further seizures is paramount (particularly those for whom driving is important or where seizures have caused significant psychosocial morbidity) and for others there is a concern about the concept of long-term medication, such that they would prefer to risk an occasional seizure, particularly if their attacks do not inconvenience them unduly. Although there are some patients (such as those with recurrent injuries due to seizures, or a tendency to status epilepticus) in whom one would strongly recommend treatment and others in whom the benefits of treatment are more doubtful, the co-operation of the patient is essential in all instances to ensure adherence.

Table 10.2 Criteria for starting AEDs.

Diagnosis of epilepsy must be firm
Risk of recurrence and nature of seizures must justify treatment
Good compliance must be likely
The patient should be fully counselled
The patient's wishes should be taken into account

Regardless of their wishes or expectations, it is important to discuss the purpose and limitations of antiepileptic drugs with people developing epilepsy. It is common, for example, for patients to expect that their seizures will be completely controlled as soon as treatment is commenced, or when a 'therapeutic' drug level is reached, whereas in practice, in 20–30% of patients, seizures may be refractory to treatment. In addition, the likely duration of treatment should be explained. Patients should be alerted to common possible adverse effects of medication, particularly skin rash: serious skin reactions can frequently be averted by withdrawing medication at the first sign of their occurrence.

Likelihood of adherence

Antiepileptic drugs must be taken reliably and regularly to maximize their efficacy and minimize the risk of withdrawal seizures. Compliance with antiepileptic medication is often poor [50], but may be improved by providing adequate counselling about the rationale for treatment, the need to take medication regularly, guidance on what to do if a dose is missed and the risk of withdrawal seizures, by the use of drugs with a low incidence of adverse effects and by simplifying the treatment regime. Adverse effects experienced early are especially likely to cause dissatisfaction, and care should be taken to build up the dose of such drugs as carbamazepine sufficiently slowly to avoid this complication. Alcohol may be another reason for poor compliance, either because of patients' concern about 'mixing' it with antiepileptic drugs, or as a result of the effects of alcohol abuse itself.

Type of epilepsy seizures or syndrome

Seizure type (characterized according to the classification of the Commission on Classification and Terminology of the International League against Epilepsy [1]) is important in determining the choice of antiepileptic drug along with the epileptic syndrome, which also affects prognosis [2]. Some types of epilepsy, such as benign childhood epilepsy with centrotemporal spikes, confer a benign prognosis, and treatment may not be required. Although generalized tonic–clonic seizures may occur in this syndrome, the attacks often take the form of simple partial seizures occurring during sleep. In contrast, in such conditions as Lennox–Gastaut syndrome, the chance of complete seizure control is likely to be small. Juvenile myoclonic epilepsy, in which myoclonic jerks, usually accompanied by generalized tonic–clonic seizures, develop during adolescence, commonly responds well to medication (particularly valproate), but carries a high risk of relapse (of the order of 90%) if medication is withdrawn.

The seizure types occurring in a particular syndrome will also guide choice of medication. Thus, while carbamazepine is a useful drug in the treatment of generalized tonic–clonic seizures, it is usually avoided if these form part of a generalized epilepsy syndrome which also includes absence seizures and myoclonic jerks, since these may be exacerbated by this drug (and also by phenytoin). The three seizure types commonly occurring in idiopathic generalized epilepsy (generalized tonic–clonic seizures, myoclonic jerks and absence seizures) are all commonly responsive to sodium valproate, while ethosuximide is effective only against generalized absence seizures. For these reasons, every effort should be made to classify the epilepsy by seizure type and syndrome, if possible.

Which drug to use

Until recently, there was a dearth of randomized controlled trials of antiepileptic drugs, leading to geographical variation in their use. Thus, phenytoin was the most commonly used antiepileptic drug in North America [51], carbamazepine was popular in the UK for seizures of partial onset, and in Italy, the drug most frequently prescribed in the FIRST study [17] following a first generalized tonic–clonic seizure was phenobarbital, which was given to 50% of the treated patients.

Valproate has traditionally been used as the drug of choice in idiopathic generalized epilepsies. In a study of standard and new antiepileptic drugs (SANAD) [52], in which valproate was compared with lamotrigine and topiramate for generalized and unclassifiable epilepsy, valproate was better tolerated than topiramate and more efficacious than lamotrigine, and was recommended as drug of first choice in many patients with these epilepsies. However, although it is often well tolerated in the short term, weight gain, hair loss and dose-related tremor may be problematic in the longer term. The issue of teratogenicity is also of major concern, with the incidence of major malformations in one study in babies of women taking valproate during pregnancy being 6.2% (95% CI 4.6–8.2%) compared with 2.2% (1.4–3.4%) for carbamazepine and 3.2% (2.1–4.9%) for lamotrigine [53]. Lamotrigine may thus be a reasonable alternative as first choice in women of child-bearing age with generalized epilepsy. The SANAD study has been criticized for including unclassifiable epilepsies with generalized epilepsies. In children with absence seizures as their sole seizure type, ethosuximide may be used. Topiramate is also licensed for the treatment of primary generalized tonic–clonic seizures in adults and children over the age of 6 years.

Carbamazepine is commonly used as drug of first choice in the UK and some other European countries for seizures of partial onset, although, as noted above, phenytoin remains popular in the USA. The SANAD study [54] randomized 1721 patients with partial epilepsy to treatment with carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. The time to treatment failure for any reason (inadequate seizure control or unacceptable adverse events) was better for lamotrigine than for any of the other drugs, largely because it had fewer adverse effects than carbamazepine, which had similar efficacy. However, it has been suggested that the target dose of 600 mg for carbamazepine might have adversely affected its tolerability when compared with lamotrigine. Levetiracetam was not included in the SANAD study, but is licensed in the UK for use as a monotherapy for the treatment of partial-onset seizures with or without secondary generalization in adults and children over 4 years of age.

The effects of carbamazepine, phenobarbital, phenytoin and primidone were compared in a randomized double-blind study of 622 adults with partial and secondarily generalized tonic–clonic seizures carried out by Mattson *et al.* [55]. The retention rate was highest with carbamazepine and phenytoin, with primidone having the worst retention rate, mainly due to adverse effects.

Carbamazepine was reported to provide significantly better total control of partial seizures (43%) than phenobarbital (16%) or primidone (16%), with phenytoin providing intermediate control (26%). A later study by Mattson *et al.* [56] compared valproate with carbamazepine for the treatment of complex partial and secondarily generalized tonic–clonic seizures in adults. The two drugs had similar efficacy in the treatment of tonic–clonic seizures, but carbamazepine gave better results for four of the five outcome measures for complex partial seizures, and was also the preferred drug when adverse effects were included in the analysis. On the other hand, in two prospective randomized studies in patients with newly diagnosed partial or primarily generalized tonic–clonic seizures carried out in the UK, one in adults [57] and one in children [58], valproate and carbamazepine were found to have virtually equivalent efficacy, a finding which applied to both subgroups of patients with partial and with generalized epilepsy, respectively.

Oxcarbazepine has been compared with sodium valproate, carbamazepine and phenytoin in separate studies of adults with newly diagnosed epilepsy. There was no statistically significant difference in efficacy between oxcarbazepine and any of the other three drugs. Comparison with carbamazepine [59] showed that oxcarbazepine caused fewer 'severe' side-effects than carbamazepine, although, again, titration of the latter was carried out relatively quickly. In the comparison of oxcarbazepine with valproate [60], there was no significant difference between the two drugs with regard to either efficacy or adverse effects. The study comparing oxcarbazepine with phenytoin [61] showed no difference between the groups with respect to the total number of premature discontinuations, but with regard to those due to adverse effects, there was a statistically significant difference in favour of oxcarbazepine. Oxcarbazepine also showed superior tolerability when compared with phenytoin in a randomized trial in children and adolescents [62].

Newer drugs are invariably more costly than the older agents available and, where health resources are limited, they must justify their use by clear benefits. It will become easier to define their place in treatment with greater experience in using them and as a result of the trials currently under way. Although the issues of teratogenicity, weight gain and possibly polycystic ovaries may lead to lamotrigine (or another new drug) being used as an alternative to valproate in women of child-bearing age, valproate remains the drug of choice in idiopathic generalized epilepsy in other circumstances, and lamotrigine or carbamazepine are appropriate choices in people with epilepsy of partial onset.

The guidelines issued by the National Institute for Clinical Excellence [63] recommend that the newer AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin), within their licensed indications, be used for the management of epilepsy in people who have not benefited from treatment with the older AEDs, such as carbamazepine or sodium valproate, or for whom the older AEDs are unsuitable because there are contraindications to the drugs, they could interact with other drugs the person is taking (notably oral contraceptives), they are already known to be poorly tolerated by the individual, or the person is a woman of child-bearing potential. In the light of the additional information now available from the SANAD study, it seems reasonable to choose either carbamazepine or lamotrigine as first-line medication for the treatment of partial-onset seizures, and valproate as first-line treatment for generalized seizures, except in women of child-bearing age, in whom lamotrigine may be a more appropriate first choice of treatment.

Women's issues

Epilepsy has specific implications for women, both on account of the effects of epilepsy and AEDs on the reproductive cycle and on the unborn child and because of the effects of pregnancy and hormonal changes on the epilepsy. The issue of teratogenicity has received considerable attention. The risk of major congenital malformations, usually estimated at around 2–3% in the general population, is increased in women taking AEDs during the first trimester of pregnancy. Several pregnancy registers have been established to estimate the relative risk for different AEDs. The UK Pregnancy and Epilepsy Register [53] found that the overall risk of a major congenital malformation was 4.2% (95% CI 3.6–5.0%): it was higher in those on polytherapy [6.0% (95% CI 4.5–8.0%)] than those on monotherapy [3.7% (95% CI 3.0–4.5%)]. The rate of major congenital malformations was significantly greater in the children of women taking valproate [6.2% (95% CI 4.6–8.2%)] than those taking carbamazepine [2.2% (95% CI 1.4–3.4%)]. The risk in babies of women taking lamotrigine was 3.2% (95% CI 2.1–4.9%). Data for other AEDs are awaited.

The possibility has also been raised that certain AEDs taken during pregnancy may adversely affect cognitive function in the unborn child. Adab *et al.* [64] found a significantly lower mean verbal IQ in children of mothers taking valproate than those taking other AEDs. Other studies have produced conflicting results about the effect of AEDs on cognition [65] and further study in this area is required.

The fact that AEDs can reduce the efficacy of the oral contraceptive pill due to induction of the hepatic cytochrome P450 system is also now widely recognized. The drugs involved include carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone and, at doses >200 mg/day, also topiramate. The chance of an unwanted pregnancy can be reduced by the use of a combined oral contraceptive pill containing at least 50 μg of oestrogen (a higher dose may be required if breakthrough bleeding occurs).

Some reports have suggested that there may be an increased incidence of polycystic ovaries in women with epilepsy taking sodium valproate [66]. At the time of writing there remains considerable debate about the general applicability of these findings. However, if proven, they may influence the future choice of AEDs in women with epilepsy, as would any difference in rates of teratogenicity between AEDs. In the event of this occurring, it would affect the choice of drug in all women of child-bearing age, including adolescents, as a high proportion of pregnancies are unplanned (56% in the community-based study of Fairgrieve *et al.* [67] of women with epilepsy).

How to start medication

In the majority of people with epilepsy, satisfactory control is achieved with a single AED, with only 10–15% of patients benefiting from polytherapy [68]. A drug appropriate to the seizure type should be chosen (Tables 10.3 and 10.4), giving preference

Table 10.3 Choosing medication for generalized seizures.

First-line drugs (used as monotherapy)
Valproate – all seizure types
Lamotrigine – generalized tonic–clonic seizures, seizures associated with Lennox–Gastaut syndrome (adults and children over 12 years)
Carbamazepine – generalized tonic–clonic seizures only (may exacerbate absence seizures and myoclonic jerks)
Ethosuximide – absence seizures only
Topiramate – generalized tonic–clonic seizures (adults and children over 6 years)
Second-line drugs (used after failure of appropriate first-line drugs)
Clobazam – adjunctive treatment for all seizure types (adults and children over 3 years)
Levetiracetam – adjunctive treatment for generalized tonic–clonic seizures and myoclonus (adults and children over 4 years)
Topiramate – generalized tonic–clonic seizures and seizures associated with Lennox–Gastaut syndrome (adults and children over 2 years if given as adjunctive treatment)
Clonazepam – all seizure types
Phenobarbital – all seizure types except absence seizures
Phenytoin – generalized tonic–clonic seizures (may exacerbate absence seizures and myoclonic jerks)

Table 10.4 Choosing medication for partial-onset seizures.

First-line drugs (used as monotherapy)
Carbamazepine
Lamotrigine
Levetiracetam
Oxcarbazepine
Topiramate
Valproate
Second-line drugs (used after failure of appropriate first-line drugs)
Clobazam – adjunctive treatment (adults and children over 3 years)
Clonazepam
Gabapentin – monotherapy and adjunctive treatment (adults and children over 6 years)
Phenobarbital
Phenytoin
Pregabalin – adjunctive treatment (adults over 18 years)
Primidone
Tiagabine – adjunctive treatment (adults and children over 12 years)
Vigabatrin – initiated and supervised by specialists, adjunctive treatment for partial seizures with or without secondary generalization not controlled by other treatment, also used in infantile spasms as monotherapy
Zonisamide – adjunctive therapy for refractory partial seizures with or without secondary generalization (adults over 18 years)

to an agent whose adverse effect profile is least likely to interfere with the quality of life of the patient. Both the dosage required to obtain a particular level of the drug in the blood and the level required to achieve control of the seizures vary from person to person, as does the level at which symptoms of toxicity are experienced. In order to minimize adverse effects, particularly acute idiosyncratic reactions and symptoms of toxicity, it is recommended that a single first-line drug for the seizure type be given in a small dose, the dose being gradually increased either until complete control of seizures is obtained or until symptoms of toxicity occur (Table 10.5). In practice, if the seizures are infrequent, such a strategy may mean prolonging the titration phase

Table 10.5 How to start AEDs.

Use a first-line drug for the seizure type
Start at a low dose
Gradually increase until seizures stop or adverse effects develop
If seizures remain uncontrolled, review the diagnosis and underlying aetiology
Substitute gradually another first-line drug for the seizure type and increase dosage until seizures stop or adverse effects develop
If necessary, try drug combinations

excessively, and in such circumstances it may be reasonable to increase the dose of medication to an 'average' dose regardless of the occurrence of seizures. For example, most adults with initially diagnosed epilepsy will respond to dosages of 400–600 mg/day carbamazepine or 600–1000 mg/day sodium valproate [69]. Measurement of serum drug levels is helpful as a guide to dosage in the case of phenytoin, which has non-linear pharmacokinetics. Drug level monitoring is occasionally helpful in the case of carbamazepine, phenobarbital and ethosuximide, but is usually unhelpful in the case of valproate and the newer AEDs.

If the patient's seizures fail to be controlled by a single AED, the diagnosis should be reviewed. The possibility of a progressive underlying aetiology should also be considered, and further neuroimaging may be warranted. If the diagnosis is confirmed, a second first-line AED for the seizure type should be added and the original drug should be gradually withdrawn. Many physicians prefer to complete the titration of the new drug before beginning withdrawal of the original medication so that any adverse effects of the drug change can be correctly attributed (although, in some cases, tolerability problems may result from drug interactions) and to avoid the situation in which the patient is receiving two drugs, both at suboptimal doses. Others, however, initiate the tapering off of the original drug whilst the second medication is being gradually introduced. Only if two first-line drugs, given individually, fail should the use of polytherapy be contemplated as a longer-term measure.

Provoking factors for seizures

If seizures are consistently provoked by specific factors, such as excess alcohol or flickering lights, it may be possible to control them without medication by avoiding the relevant stimuli. However, most patients will have some spontaneous seizures in addition to the provoked events, and will therefore require AEDs.

Excess alcohol intake (or its abrupt withdrawal) was thought to be the cause of seizures in 6% of patients registered with the National General Practice Study of Epilepsy [70], and was particularly common in people between the ages of 30 and 39 years, in whom it was responsible for 27% of cases. Drug treatment may be particularly difficult in such patients: adherence is likely to be poor and the adverse effects of alcohol and AEDs on the liver may be additive. Sleep deprivation can also precipitate seizures in susceptible individuals and may be associated with alcohol abuse. Stress, fever or other illness, sleep, heat, flashing lights and, in women, menstruation were identified as seizure

precipitants by patients undertaking a survey at a tertiary care centre [71]. Certain drugs, including most antidepressants and other psychotropic agents, lower the seizure threshold; however, although this may influence choice of drug it is important that mental health disorders are treated appropriately, despite the epilepsy. Withdrawal of benzodiazepines and other sedatives should be undertaken slowly to avoid withdrawal seizures.

Photosensitivity, in which generalized epileptic discharges occur in response to intermittent photic stimulation, occurs in about 5% of people with epilepsy. It is seen particularly in people with idiopathic generalized epilepsy (often developing in childhood or adolescence) but also occurs in some people with occipital epilepsy. The risk of seizures occurring as a result of photosensitivity may be reduced by using a small television screen and increasing the viewing distance, using a remote control to change channels, closing one eye or using polarized spectacles and reducing the screen contrast and brightness.

Other counselling

Education of the person developing epilepsy is an important part of the initial management (Table 10.6 provides an example of a counselling checklist). Epilepsy nurse practitioners, and also epilepsy societies, may be helpful in reinforcing the information provided by the physician and providing written information. The diagnosis of epilepsy carries significant implications for work and leisure, as discussed above, but is also a frightening experience leading to loss of confidence, and often a reluctance to undertake normal daily activities [72].

Information provided to the patient should explain the nature of epilepsy, its causes and the purpose of the various investigations performed (many patients are confused, for example, by the fact that they are diagnosed as having epilepsy despite having a normal EEG). First aid measures for treating seizures should be discussed with the patient and those relatives and friends for whom they deem it appropriate. The risks of seizures (including SUDEP) should be addressed in a sensitive manner, and measures to prevent injury (such as the avoidance of unguarded heights, unguarded fires, swimming alone) in the event of a further seizure discussed. Driving laws vary from country to country, and the patient must be educated about the relevant regulations and of the need to inform the driving authorities, where it is incumbent on them to do so. The need to lead as normal a life as possible within the confines of taking reasonable care, however, should be emphasized: most sports are possible, though some, such as boxing, wrestling, pot-holing and scuba diving, should be avoided.

The issues relating to drugs mentioned above should be discussed. In some countries, patients with epilepsy are eligible to receive free medication. The possibility of interactions with other drugs, especially the oral contraceptive pill, is of particular importance. Patients should be advised to avoid excess alcohol, sleep deprivation and other factors likely to precipitate seizures: on the other hand, they should be reassured in the case that, for example, photosensitivity is *not* an issue. The risk of teratogenicity should be discussed with girls and women of child-bearing age, as should the importance of planning any pregnancy, prior medication review, and the addition of folic acid before pregnancy and for the first trimester.

Some occupations, particularly those requiring a driving licence, or those in which the person with epilepsy has sole responsibility for the safety of another, may not be possible. However, for many, employment can continue to be safely undertaken, particularly with education of the employer. It is important that children with epilepsy be treated in a similar manner to other children, except for simple safety measures to avoid injury; the morbidity attributable to overprotection and underexpectation of such children is often considerably greater than the effect of the seizures themselves. Adequate schooling is also important; it is usually possible for children suffering seizures to rejoin their class after a short recovery period, rather than being sent home on each occasion. On the other hand, teachers and parents should be alert to the possible effects of ongoing epileptic discharges and of AEDs on cognition, with appropriate action being taken if these occur.

Table 10.6 Counselling checklist for people developing epilepsy.

Nature of epilepsy
First aid management of seizures
Avoidance of precipitating factors, including alcohol and sleep deprivation
Purpose of medication, and likely duration
Nature of common adverse effects of medication
Need to take medication regularly
Risks of seizures and advice regarding common hazards
Laws regarding driving
Interaction with other drugs, especially oral contraceptive pill (where relevant)
Possibility of teratogenicity, where relevant

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11 Management of Chronic Active Epilepsy in Adults

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Chronic active epilepsy can be defined as *epilepsy in which seizures are still occurring 5 or more years after the initiation of therapy*. Chronic epilepsy is more difficult to treat than newly diagnosed epilepsy, a fact that has been clearly noted by and interested researchers for at least 150 years. William Aldren Turner, for instance, in 1907 [1], noted in his series of 366 new cases of epilepsy that initial remission occurred in about 50% on therapy (usually with bromide) and long-term remission (effectively a 'cure') in 23.5%. However, by the time epilepsy had persisted and become chronic, he found that the use of bromide was far less successful and indeed 'had relatively little value', and, although drugs often reduced the frequency of seizures, long-term seizure remission was uncommon. Because of this, he emphasized the importance of early diagnosis and early treatment, and indeed went further by recognizing a 'prodromal stage' before seizures actually developed, in which therapy could be preventative. His observations on the relatively good response to therapy in new patients, in contrast to the poorer response in chronic active cases, has been repeatedly confirmed on many occasions since.

In a review of prognosis in epilepsy in 1984 [2], it was pointed out that the most important single predictor of prognosis (in non-syndromic epilepsy) was the temporal stage the epilepsy had reached (i.e. the length of time that epilepsy had been active). It was demonstrated, *inter alia*, that with contemporary therapy: (1) the prognosis in newly diagnosed epilepsy was excellent; (2) the prognosis in chronic established epilepsy was much less good; (3) the longer the epilepsy remained active, the less likely was seizure control to be achieved; and (4) the longer-term prognosis could be, to a large extent, predicted from the course of epilepsy in the few years from the onset of therapy. These points have also been repeatedly confirmed since. In a paper in 1986 [3], it was also shown that the patterns of seizures over time was relatively consistent and that epilepsy tended to run 'true to form'. Whether this is still the case, in an era in which drug therapy has greatly expanded, is questionable and needs to be further researched.

Although it is clear that the response to therapy in new cases is excellent, and better than in chronic cases, this does not mean that the response to therapy in chronic epilepsy or prognosis is necessarily poor [4–7]. A substantial number of patients obtain worthwhile seizure reductions on therapy and a smaller number obtain prolonged remissions, albeit on therapy. In many, quality of life can be greatly improved by appropriate therapy. Furthermore, the term chronic epilepsy encompasses a wide range of different conditions, syndromes and aetiologies. Some syndromes have an almost inevitably poor prognosis, but in others, prolonged remission is to be expected (the treatment of specific syndromes or aetiologies is not covered in this chapter, but is described in other chapters in section 2 of this book). Severity also varies, and patients with mild epilepsy, even if chronic, are not necessarily inconvenienced by the condition and may not require therapy. The response to therapy also depends on age and on aetiology (and these aspects too are described elsewhere in this section). However, the prospect of 'cure' is still, for most adult patients with chronic epilepsy, elusive.

Extent of response to therapy in chronic active epilepsy

In the last 18 years, 14 new antiepileptic drugs have been licensed, all of which have shown unequivocal efficacy in clinical trials (Table 11.1). This greater range of therapies might be expected to have influenced prognosis. Indeed, this seems very likely to be the case, although no recent large-scale long-term studies in unselected populations have been carried out to confirm this. Reduction in seizure numbers or seizure severity is commonly the result of the introduction of previously untried medications (and this has been demonstrated in controlled and randomized clinical trial settings as well as in large-scale clinical studies, including studies of retention of therapy). Furthermore, in several recent hospital-based studies, in selected populations of patients with chronic epilepsy, it has been shown that a substantial number of patients whose epilepsy is not initially controlled can achieve long-term remission on the introduction of newer therapies. In a study of 155 patients with chronic epilepsy (often severe), a change of drug therapy resulted in seizure remission (defined as a 12-month or longer period without seizures) in 28% [7]. It is likely that this encouraging response is, at least in part, due to the greatly increased range of different antiepileptic drugs now available, and indeed, in this group, over an observation period of 5 years or so, even if the first change did not result in seizure response, when a second drug introduction was made, a further 14% of the patients who failed at first change attained seizure freedom, and 15% after a third change in those who failed after a first and second change. The authors concluded that it was incorrect to view intractability as inevitable if seizure control is not obtained with initial medication or within a few years of the onset of therapy. The drug most commonly started in this study was levetiracetam (in 101 patients), but other new drugs also resulted in seizure freedom, as one would expect from the findings of clinical trials. In this study, 25% became seizure free (defined as in remission on the drug at the

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Table 11.1 Drugs licensed in Europe and/or the USA since 1989.

Year of first licence	Proprietary name	Country in which first licensed	Manufacturer
1989	Vigabatrin	UK	Marion Merrill Dow
1990	Lamotrigine	Ireland	Burroughs-Wellcome
1990	Oxcarbazepine	Denmark	Novartis
1993	Felbamate	USA	Carter Wallace
1994	Gabapentin	USA, UK	Parke-Davis
1995	Topiramate	UK	Johnson and Johnson
1996	Tiagabine	France	Novo-Nordisk
1999	Levetiracetam	USA	UCB Pharma
2000	Zonisamide[a]	USA	Elan pharmaceuticals
2004	Pregabalin	European Union	Pfizer
2007	Stiripentol	European Union	Laboratoires Biocodex
2007	Rufinamide	European Union	Eisai
2008	Lacosamide	European Union	UCB Pharma

[a]Zonisamide was licensed in 1989 in Japan and South Korea as Excegran (manufactured by Dainippon Pharmaceuticals).
From Shorvon SD. A history of the drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959–2009. *Epilepsia* 2009; **50** (in press).

time of last appointment and follow-up for at least 12 months) [8]. More recently, Callaghan *et al.* [9] reported a series of 246 patients with chronic active epilepsy (having at least one seizure per month and having not responded positively to at least two antiepileptic drugs) and followed the cases prospectively for 3 years in the clinic. Nineteen per cent were in 6-month terminal seizure remission. Similar findings were made by others.

There is a regrettable tendency in many clinics to offer no new therapy when faced with a patient with chronic epilepsy, and this should be resisted. As these studies show, it is important to take an active and explorative approach to drug therapy in these patients (and there are many), in whom the search for seizure freedom is the major priority. The application of a systematic protocol to the treatment of chronic epilepsy will improve seizure control in a substantial proportion of cases.

Intractable (refractory) epilepsy and drug resistance

The term 'intractable' (or refractory) epilepsy is widely used, but difficult to define. It is, of course, a retrospective definition and a 'prediction'. As new therapy is introduced, the seizures in some patients with hitherto refractory epilepsy become controlled, as they do after successful epilepsy surgery. It is arbitrary as there are at least 10 first-line antiepileptic drugs for refractory partial seizures, and far more combinations: with 10 first-line antiepileptic drugs there are 45 different two-drug and 36 different three-drug combinations. All combinations cannot, therefore, be tried. It seems appropriate to use different definitions for different purposes, as suggested by French and colleagues [10,11]. An excellent suggestion is to define intractability by the number of ineffective drugs tried; thus second-level intractability is defined as the failure of two drugs, third-level intractability by the failure of three drugs, and so on [12].

However, whatever definition is used, all are agreed that there are identifiable clinical factors which allow some sort of prediction to be made. In non-syndromic adult epilepsy, the prognosis is generally worse in the presence of frequent seizures, mixed seizure types, additional intellectual impairment, structural pathologies, pathologies with a large extent, cortical pathologies (especially in frontal and temporal regions), additional neurological handicaps or severe psychiatric disorder. To what extent each of these factors worsens prognosis has not been fully established, and there are many patients with chronic epilepsy who present to epilepsy clinics in whom an accurate prediction of prognosis is not possible. Some of the individual childhood syndromes have well-defined and consistent prognoses, both good and bad.

Another simplistic concept is that drug resistance is, at least to an extent, a unitary concept genetically based and related to genetically determined variations in cerebral drug transporters or drug targets (see Chapter 8). In other words, single polymorphisms will be present which if identified could be used to predict response to therapy. Although an initially attractive hypothesis, this theory ignores the variation in other factors. Drug response is clearly affected, for instance, by aetiopathology (i.e. the aetiology, extent or location of lesions), by physiology (type of seizures, physiological basis, syndrome), in the type of medication (different drugs work by different mechanisms) or in other medicinal aspects (dose, serum level, interactions) and by variation over time (brain maturation, time-linked expression of epilepsy, seizure type or syndrome). For these reasons, it seems highly unlikely that a single pharmacogenetic mechanism will be found to account for drug resistance and to be useful in predicting drug response except in exceptional circumstances. Another curious fact about resistance is that it may develop after a long period of remission. In a study by Berg *et al.* [13] 26% of 33 patients presenting for epilepsy surgery reported a previous period of remission (1–28 years). Similarly, as shown above, long remission can occur in previously intractable epilepsy.

Treatment approach for chronic active epilepsy in adult patients

As mentioned above, there are many different types of epilepsy, and the management can vary, especially in children. A detailed description of therapy in childhood epilepsy and in specific epilepsy syndromes and aetiologies can be found in other chapters in Section 2 of this book. Here, the approach to therapy in a typical case of non-syndromic adult chronic epilepsy is outlined, as these cases make up the bulk of those attending specialist epilepsy clinics worldwide. Of course, individuals have different requirements and therapy should be tailored to individual need. Nevertheless, broad principles apply to most cases, and these are the subject of this section. In such cases, the approach to management is divisible into two clearly distinct phases: assessment and treatment (Table 11.2).

Assessment

Faced with a new presentation of chronic epilepsy, the physician should gather and document information which will form the basis of future recommendations for treatment. The following factors should be assessed – this list of factors is not exhaustive but is the minimum required before considering therapy.

Confirming the diagnosis of epilepsy

It may be surprising to know that 20% or more of patients referred to neurology clinics with chronic epilepsy do not in fact

Table 11.2 Principles of treatment in chronic active epilepsy.

Assessment
Review diagnosis and aetiology (history, EEG, imaging)
Classify seizures and syndrome
Review compliance
Review drug history
Which drugs were useful in the past
Which drugs were not useful in the past
Which drugs have not been used in the past
(also dose, length of therapy, reasons for discontinuation)
Review precipitants and non-pharmacological factors
Review co-morbidities
Treatment plan
Decide and document proposed sequence of drug 'trials'
Decide what background medication to continue
Decide upon the sequence of drug additions and withdrawals
Decide the duration of drug 'trials'
Decide when to do serum level monitoring
Consider surgical therapy
Consider non-pharmacological measures (lifestyle, alternative therapy, etc.)
Recognize the limitations of therapy
Counsel and provide information on the above points to patients

Table 11.3 Methods of improving compliance.

Information about drug treatment
Role, limitations, efficacy, side-effect
Drug therapy
Monotherapy, simplify regimen, introduce drugs slowly
Aide-memoire
Drug wallet, regular remainders, cues
Reinforcement at regular clinic follow-up visits

suffer from epilepsy at all [14]. Many different conditions may be confused with epilepsy, but the most common are psychogenic seizures, reflex syncope and cardiac arrhythmia. The differential diagnosis of epilepsy is discussed in detail in Chapter 4. As emphasized there, an eye-witness account of the attacks should be obtained and will usually be diagnostic. If there is any doubt, the previous medical records should be inspected and attention paid to previous electroencephalograms (EEGs). A series of normal EEG results should alert one to the possibility that the attacks are non-epileptic, although this is not an infallible rule. A video recording of an attack is extremely helpful in deciding its aetiology – and many patients are able to have their attacks recorded on a camcorder or a mobile phone. Such recordings often obviate the need for video-telemetry and it is surprising how often a short amateur recording is diagnostic.

Establishing the aetiology of the seizures

The cause of the epilepsy must be established. Specific cerebral conditions may require therapy in their own right, and prognosis and response to therapy are strongly influenced by cause. A summary of the causes of epilepsy is given in Chapter 3. A high-quality MRI scan is a mandatory test in an adult patient with chronic epilepsy without a known cause, and not infrequently will reveal a previously undetected cause [15,16]. The therapy of epilepsy is often uninfluenced by the cause but establishing a cause almost always makes the clinical management of a patient with chronic epilepsy easier and allows a more accurate prognosis to be made, which in its turn influences how active the therapeutic approach should be.

Classifying seizure type and syndrome

As is noted repeatedly throughout this book, epilepsy is a highly heterogeneous condition, and varies considerably in form and severity. It is important to classify formally the seizure type and, where appropriate, the epilepsy syndrome, as these classifications will guide the choice of medication. This will often require electroencephalography. The choice of drug for each seizure type is discussed in detail in Chapter 30.

Documenting previous treatment history

The response to an antiepileptic drug is often relatively consistent over time. A knowledge of the previous treatment history, therefore, is vital to the formulation of a rational treatment plan (see Treatment, below). This aspect of assessment is commonly ignored and yet is of the greatest importance. It is important to ascertain what previous drugs have been tried, at what dose (if possible), for how long, in what combinations and with what result. The reasons for discontinuation should be defined.

Reviewing compliance

Poor compliance can also be a reason for poor seizure control, and it is important to ascertain how adequate drug-taking has been. A drug should not be presumed to be ineffective if it was taken erratically. Methods for improving compliance are listed in Table 11.3.

Identifying and treating other factors and co-morbidities

The co-morbidities of epilepsy can influence markedly the response to therapy. The medical and psychiatric co-morbidities are summarized and their effects on therapy are discussed in detail in Chapters 20 and 21.

Treatment

Treatment of chronic epilepsy (as all epilepsy) should be based on balancing the benefits of therapy against the potential risks – and where to strike this balance is a personal decision for each patient. The role of the physician in this regard is to provide estimates of the potential benefits and risks and to discuss these with the patient [17].

The key step is the formulation of an *antiepileptic drug treatment plan*. This plan should be based on the assessment. The plan should take the form of a stepwise series of treatment trials, each to be tried in turn if the previous trial fails to meet the targeted level of seizure control. The plan should be devised to trial suitable antiepileptic drugs in turn, in a reasonable dose, singly or as two-drug (or more rarely three-drug) combinations. The sequence of drugs to be tried should be clearly documented and discussed with the patient.

Such a planned sequence of drug changes can take months to complete and requires patience and tenacity. The procedure should be explained in advance to the patient to maintain

confidence and compliance. Ideally, each antiepileptic drug should be tried in a reasonable dose added to a baseline drug regimen (usually one or two other antiepileptic drugs) which does not change. The duration of the trial will depend largely on seizure frequency, and the higher the frequency the shorter the trial. This topic is discussed further in Chapter 9.

In formulating a plan, decisions have to be made about the therapeutic target (i.e. seizure freedom, seizure reduction, side-effect reduction), which drugs to trial and in what sequence, which drugs to retain as a baseline regime, which drugs to withdraw and the duration of each treatment trial.

Choice of drug to trial

The choice of drugs is discussed in detail in Chapter 30. The drugs should be selected on the basis of seizure type/syndrome (Table 30.2), and other considerations covered in Chapter 30. The drug should usually be one that has not been used before, or not previously used in optimal doses, or which has been used and did prove helpful. Rational choices depend on a well-documented history of previous drug therapy. The initial dose and maximum incremental increases in dose in routine practice are shown in Chapter 9 (Table 9.2).

Drug choice is an individual decision for a patient to make and will depend on potential side-effects and other factors. People differ in their willingness to risk adverse effects, or to try new therapy, and patients' preferences depend on such aspects as age, gender, co-morbidity, co-medication, drug formulation and dosing frequencies, risks in pregnancy and a range of social aspects. Cost is also a consideration in some health-care settings (Table 11.4).

Choice of drug to retain as the baseline regime

It is usual to aim for therapy with either one or two suitable antiepileptic drugs. If drugs are being withdrawn, it is wise to maintain one drug as an 'anchor' to cover the withdrawal period.

Table 11.4 Factors influencing choice of treatment regimen in epilepsy.

Personal patient-related factors
Age and gender
Co-morbidity (physical and mental)
Social circumstances (employment, education, domestic, etc.)
Emotional circumstances
Attitude to risks of seizures and of medication
Factors related to the epilepsy
Syndrome and seizure type
Severity and chronicity
Aetiology (less important in chronic epilepsy)
Factors related to the drug
Mechanism of action
Strength of therapeutic effects
Strength and nature of side-effects
Formulation
Drug interactions and pharmacokinetic properties
Cost

This list illustrates the sort of factors which influence drug choice. It is not comprehensive, and the importance of factors will vary from individual to individual. A more detailed treatment of this topic is covered in Chapter 30.

The advantages and place of monotherapy versus polytherapy are discussed in Chapter 9.

Drug withdrawal

Drug withdrawal needs care. The sudden reduction in dose of an antiepileptic drug can result in a severe worsening of seizures or in status epilepticus – even if the withdrawn drug was apparently not contributing much to seizure control. Why this happens is not clear. Experience from telemetry units suggests that most withdrawal seizures have physiological features similar to the patient's habitual attacks. It is therefore customary, and wise, to withdraw medication slowly. This caution applies particularly to barbiturate drugs (phenobarbital, primidone), benzodiazepine drugs (clobazam, clonazepam, diazepam) and to carbamazepine. The fastest decremental rates that are recommended in normal clinical practice are shown in Chapter 9 (Table 9.2). In many situations, even slower rates of withdrawal are safer and to be preferred. The only advantages to fast withdrawal are better compliance and the faster establishment of a new drug regimen.

Only one drug should be withdrawn at a time. If the withdrawal period is likely to be difficult, the dangers can be reduced by covering the withdrawal period with a benzodiazepine drug (usually clobazam 10 mg/day), given during the phase of active withdrawal. A benzodiazepine can also be given if there is clustering of seizures following withdrawal.

It is sometimes difficult to know whether seizures during withdrawal are a result of the withdrawal or simply the background epilepsy. Whenever possible, a long-term view should be taken and over-reaction in the short-term reaction to seizures should be avoided.

Sometimes the simple withdrawal of a drug will result in improved seizure control by reducing side-effects, assuring better compliance, and reducing drug interactions.

Drug addition

New drugs added to a regimen should also be introduced slowly, at least in the routine clinical situation. This results in better tolerability, and is particularly important when adding benzodiazepines, carbamazepine, lamotrigine, levetiracetam, primidone or topiramate. Too fast an introduction of these drugs will almost invariably result in side-effects. It is usual to aim initially for a low maintenance dose but in severe epilepsy higher doses are often required.

Concomitant medication

Changing the dose of one antiepileptic (either an increment or a decrement) can influence the levels of other drugs, and the changing levels of concomitant medication can contribute to changing side-effects or effectiveness.

Limits on therapy

Drug therapy will fail in about 10–20% of all patients developing epilepsy, and a higher proportion of those with chronic epilepsy. The goal of therapy in these cases is not seizure freedom but the best compromise between inadequate seizure control and drug induced side-effects. Individual patients will take very different views about where to strike this balance.

Table 11.5 Topics for information provision and counselling for all patients with epilepsy.

Nature of epilepsy
First aid management of seizures
Avoidance of precipitating factors, including alcohol and sleep deprivation
Purpose of medication, and likely duration
Nature of common adverse effects of medication
Need to take medication regularly
Risks of seizures (including SUDEP) and advice regarding common hazards
Legal aspects of driving
Interaction with other drugs

Serum level monitoring

For drugs whose effectiveness and/or side-effects are closely linked to serum level – notably phenytoin, carbamazepine and phenobarbital – measurement of the serum level can be helpful in deciding dosage. Monitoring serum level is particularly important in the case of phenytoin, which has a non-linear relationship between dose and serum level.

Drug interactions are another important aspect of therapy with antiepileptic drugs. They are common and important interactions with other antiepileptic and non-antiepileptic drugs [18,19]. These mostly occur in response to inhibition and induction of hepatic enzymes and affect mainly those drugs metabolized by the cytochrome P450 system or uridine diphosphate–glucuronosyltransferase (UGT) enzymes, but increasingly complex interactions at other sites are also recognized. The antiepileptic drugs that are most likely to be involved in drug–drug interactions are carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate, tiagabine, valproate and zonisamide.

The usual indications for serum level monitoring are listed in Chapter 9. These are to assess blood levels where there is a poor therapeutic response in spite of adequate dosage; identify the cause of adverse effects where these might be drug induced; measure pharmacokinetic changes in the presence of physiological or pathological conditions known to alter drug disposition (e.g. pregnancy, liver disease, renal failure, gastrointestinal disease, hypoalbulinaemic states); identify and minimize the consequence of adverse drug interactions in patients receiving multiple drug therapy; identify poor compliance; and identify the possibility of level changes owing to change in formulation.

Counselling and information provision

Counselling should be offered for chronic patients, as for all patients, on the topics listed in Table 11.5. Those with chronic active epilepsy, however, have additional problems: fears about the risks of future seizures, anxiety about the stigmatizing effects of epilepsy, and its effects on employment, self-esteem, relationships, schooling and leisure activities. The areas in which the condition impacted were demonstrated in one large survey of 1652 persons on treatment with epilepsy in Britain [20], summarized in Table 11.6. Many of these could be ameliorated by appropriate counselling and these topics should be addressed. The issues depend on age and the severity of epilepsy. A more detailed consideration of counselling is given in Chapter 26.

Table 11.6 The CSAG study of epilepsy (2001): survey of the impact of epilepsy on young adult patients and on elderly patients with epilepsy. In the course of a questionnaire study of their epilepsy, patients were asked to list areas in which epilepsy caused major impacts on their lives.

(a) Patients aged 17–65 years

Patients with mild seizures (568 patients returned a questionnaire; impacts reported = 1140)		Patients with severe seizures (347 patients returned a questionnaire; impacts reported = 842)	
Area	Patients reporting a major impact in this area (%)	Area	Patients reporting a major impact in this area (%)
Driving ban	48	Work	51
Work	36	Psychological	35
Social life	19	Social life	32
Psychological	18	Driving ban	28
Loss of confidence	8	Supervision	10
None	11	Independence	9

(b) Patients > 65 years

Patients with mild seizures (127 patients returned a questionnaire; impacts reported = 191)		Patients with severe seizures (28 patients returned a questionnaire; impacts reported = 57)	
Area	Patients reporting a major impact in this area (%)	Area	Patients reporting a major impact in this area (%)
Driving ban	32	Driving ban	39
Psychological	19	Psychological	29
Work	14	Seizures	21
Bad memory	9	Work	21
None	19	Social life	14
		Loss of self-confidence	11
		Mobility	11
		Supervision	11

From ref. 20.
Patients' seizures were divided into mild or severe on the basis of frequency and score on the National Hospital Seizure Severity Scale.
CSAG, Clinical Standards Advisory Group.

Epilepsy surgery

Resective or functional surgery for epilepsy should be considered in any patient with epilepsy not responding to drug therapy and if the potential benefits are considered to outweigh the potential risks [21–23]. This assessment is complex and presurgical evaluation should be carried out in an experienced epilepsy surgery unit. The elements of assessment are given in section 4 of this book, and an overview of presurgical assessment in Chapter 60. It is a multidisciplinary process, involving neurologist, neurosurgeon, psychologist, psychiatrist, neurophysiologist and radiologist. Onward referral to a specialized unit should be made for all patients in whom surgery is considered an option.

Drug treatment of chronic active epilepsy in the elderly

About 30% of new cases now occur in people over 65 years and, currently, about 0.7% of the elderly population are treated for epilepsy, making epilepsy the third most common neurological condition in the elderly after dementia and stroke. As the number of elderly people in the population is rising, the numbers of elderly people requiring treatment for epilepsy is also greatly increasing. The chief cause of epilepsy in those over 65 years is cerebrovascular disease. Diagnosis is not always easy, and care must be made to differentiate epilepsy from cardiac arrhythmia, syncope, vascular disease, transient global amnesia, vertigo and non-specific 'funny turns'.

The specific problems of treating epilepsy in the elderly are covered in Chapter 16, but, here, a brief outline will be given of some of the salient points. The general principles of treatment in the elderly are similar to those in other adults, but there are potential differences which deserve special mention.

Pharmacokinetic differences

The pharmacokinetic properties of many AEDs are not only different in the elderly, but the degree of pharmacokinetic variability is greater [24]. There are changes in absorption, protein binding, metabolic metabolism and renal clearance. The last is almost always lower in the elderly than in young adults, and the glomerular filtration rate declines by a mean of over 50% between the age of 30 and 80 years. The volume of distribution for lipid-soluble drugs is increased and the clearance often lowered owing to renal or hepatic disease. The half-life of many drugs is thereby increased.

Reference ranges

The 'reference ranges' of AEDs are somewhat lower in the elderly. The reasons for this are not clear, but presumably reflect pharmacodynamic changes.

Drug interactions

Drug interactions are common [25]. In the USA, persons over the age of 65 constitute 13% of the population yet receive 32% of prescribed medications. In one study of patients with epilepsy over 65 years old in the USA, a mean of 5.6 medications (antiepileptic and non-antiepileptic) per patient were taken [26].

Co-morbidities

Co-morbidities also are common, and most patients over the age of 65 years have other conditions treated by other drugs, with a marked potential for pharmacological and clinical interactions with epilepsy.

Choice of drugs

Choice of drugs is discussed at length in Chapter 16. Suffice to say here that both the antiepileptic effect and particularly the range of side-effects (and the doses and drug levels at which side-effects occur) can be quite different in the elderly. Whatever therapy is chosen, it is usual to start therapy at half the young adult dose and to increment the dose at half the young adult titration speed. Compliance can be poor. Careful clinical and pharmacological monitoring is essential.

For all these reasons, where possible therefore, therapy should be informed by studies conducted specifically in the elderly. Often data are lacking, and this is unsatisfactory.

Drug treatment of chronic active epilepsy in women

There are specific aspects of treatment which apply to women but not to men. These are considered in greater depth in Chapter 25 but will be considered here in outline.

Fertility

Fertility rates have been shown to be lower in women with treated epilepsy than in an age-matched control population. In one study of a general population of 2 052 922 persons in England and Wales, an overall fertility rate was found of 47.1 (95% CI 42.3–52.2) live births/1000 women with epilepsy per year compared with a national rate of 62.6. The difference in rates was found in all age categories between the ages of 25 and 39 years [27]. There are many possible reasons, including social, environmental and genetic factors. However, antiepileptic drug therapy might be a contributing factor and some workers have found an association between valproate therapy and polycystic ovarian syndrome [28]. The findings are controversial and not consistently duplicated.

Contraception

This topic is well reviewed by O'Brien *et al.* [29].

Combined oral contraceptive

There is no reason why women with chronic epilepsy on therapy with antiepileptic drugs should not take the combined oral contraceptive. However, drugs that induce hepatic enzyme activity (particularly CYP3A family enzymes: barbiturate, phenytoin, primidone, oxcarbazepine and carbamazepine) increase the metabolism of the oestrogen and progesterone components of the pill (sometimes by 50%) thereby reducing its efficacy. Topiramate lowers the level of oestrogen by 30% by a different mechanism. Lamotrigine may also affect the efficacy of the combined contraceptive pill and co-medication with the pill also affects lamotrigine levels (by 40–60%). To achieve contraceptive protection, therefore, patients co-medicated with enzyme-inducing antiepileptic drugs usually either need to take a pill with a higher oestrogen content (>60 μg) or double their dose of the lower oestrogen pills or tri-cycle the pill (taking three monthly packets of the contraceptive without a break, followed by an interval of 4 days rather than the usual 7). Despite the well-known risks of drug interaction, the inappropriate prescribing of low-dose contraceptive with enzyme-inducing drugs is widespread. In a large UK general practice survey, 17% (390 out of 2341) of all women with epilepsy were on an oral contraceptive. Of these, 200 were co-medicated with an enzyme-inducing antiepileptic drug, and 44% (87 out of the 200) were taking a contraceptive pill with less than 50 μg of oestradiol.

Other forms of contraception

The progesterone-only pill (the 'mini-pill') is affected in a similar manner to the combined contraceptive. Medroxyprogesterone acetate (Depo-Provera) has no interactions with antiepileptics, as there is virtually 100% clearance on first pass through the liver, and enzyme induction should have no effect. The progestogen implant (Implanon) is affected by enzyme-inducing drugs, and so should not be used. Postcoital contraceptives are also affected by enzyme-inducing antiepileptic drugs, and so the first dose should be doubled and a second single dose given 12 h later. Intrauterine contraceptives are not affected by enzyme-inducing drugs.

Menstruation and catamenial epilepsy

Epilepsy in which the seizure pattern has a strong relationship to the menstrual cycle is referred to as catamenial epilepsy. There have been attempts to devise special treatment approaches to patients with catamenial seizures, but these are generally unsuccessful. Strategies tried include hormonal manipulation and the abolition of the menstrual cycle by hormonal means or even oophorectomy. A widely used approach in chronic active epilepsy is to intensify antiepileptic drug therapy around menstruation. Five to seven days' therapy with diuretics, acetazolamide and clobazam has been tried. In routine clinical practice, these produce a worthwhile effect in only a small number of women.

Drug treatment of chronic active epilepsy during pregnancy

Of all the specific therapeutic issues encountered in an epilepsy clinic, perhaps the most difficult and uncertain relate to therapy in pregnancy. About 3–4 live births per 1000 women of childbearing age with epilepsy occur each year. Therapy in this situation, more than in others, needs to be carefully tailored to the individual – and counselling is imperative.

Teratogenicity and antiepileptic drugs

This topic is covered in depth in Chapter 25. Here, a summary will be given, especially as this relates to chronic active epilepsy. It is the area of greatest concern and also the most difficult in which to give sound advice.

Major malformations associated with antiepileptic drugs

The most common major malformations associated with traditional antiepileptic drug therapy (phenytoin, phenobarbital, primidone, benzodiazepine, valproate, carbamazepine) are cleft palate and cleft lip, cardiac malformations, neural tube defects, hypospadias and skeletal abnormalities. The risk of spina bifida has been particularly well studied. The background population risk of spina bifida is approximately 0.2–0.5% with geographic variation. Valproate is associated with a 1–2% risk of spina bifida aperta, a risk that is strongly dose related. Carbamazepine carries a risk of spina bifida aperta of about 0.5–1%. Both carbamazepine and valproate have been associated also with hypospadias. The overall risk of malformations was thought previously to be particularly high because of phenytoin exposure, although recent studies of phenytoin monotherapy have shown a very low incidence of major defects – and it may be that the previously high rates were attributable to polytherapy and exposure to high levels at a time when blood level control was not available. However, phenytoin therapy has been clearly associated with an increased risk of neuroblastoma in the infant, although the absolute risk is very small. One study purported to demonstrate smaller head circumference in babies of mothers on carbamazepine, but the statistical basis of this observation was not well founded. Small increases in pre- and postnatal growth retardation rates have been found in controlled studies of mothers taking antiepileptic drugs, but the growth differences had disappeared by the time the offspring were 5 years old.

Other developmental abnormalities

In addition to the major malformations, less severe dysmorphic changes ('fetal syndromes') have been postulated, although there is little agreement about their frequency or indeed even their existence. The problem is further complicated by the confounding influences of socioeconomic and genetic factors. The fetal phenytoin syndrome was the first to be described, and is said to comprise a characteristic pattern of facial and limb disturbances (Table 11.7). Most of these features though are minor and

Table 11.7 Some features reported to occur in fetal anticonvulsant syndromes.

Growth
Pre- and postnatal growth deficiencies
Microcephaly
Craniofacial
Short nose, low cranial bridge
Hypertelorism
Epicanthic fold
Strabismus and other ocular abnormalities
Low-set ears and other aural abnormalities
Wide mouth, and prominent lips
Wide fontanelles
Cleft palate and cleft lip
Limbs
Hypoplasia of nails
Transverse palmar crease
Short fingers
Extra digits
Cerebral
Learning disability
Developmental delay
General
Short neck, low hairline
Rib, sternal and spinal anomalies
Widely spaced hypoplastic nipples
Hernias
Undescended testicles
Neuroblastoma and neural ridge tumours
Cardiac and renal abnormalities
Hypospadias
Neural tube defects

This is a list of reported abnormalities, although many are uncontrolled observations and the frequency of the anomalies is unclear (indeed some may be no more frequent in exposed and unexposed infants). The contribution of antiepileptic drugs is also unclear, and genetic, environmental and socioeconomic factors may also play a role in their development.

overlap with the normal variation seen in children born to healthy mothers. Recent prospective and blinded studies have shown that only hypertelorism and distal digital hypoplasia occurred at any greater frequency, and even these associations are weak. Furthermore, the nail hypoplasia tends to disappear during childhood. A carbamazepine syndrome, primidone and phenobarbital syndromes and valproate syndrome are also reported.

Even greater controversy exists in relation to the question of whether maternal drug usage results in developmental delay and learning disability. Although there is no doubt that these occur at a higher frequency among infants born to epileptic mothers (between two- and sevenfold increases), the association could be due to genetic, environmental or socioeconomic factors. A recent study showed that 41 children exposed to valproate monotherapy had significantly lower verbal IQ (VIQ) scores than 52 children exposed to carbamazepine and 21 to phenytoin monotherapy. Low VIQ was also associated with the occurrence of five or more tonic–clonic seizures during pregnancy. There were also higher rates of dysmorphic features in the valproate-exposed children, and these were most common in those with low VIQ scores. Some caution needs to be exercised in interpreting these results: the study was a retrospective survey, the mothers were not randomized to different monotherapies, there was only a 40% response rate, and there are some inconsistencies, for instance, the fact that significant differences in VIQ rates were not found in fetuses that were exposed to valproate polytherapy and there was not a significant dose–response relationship.

When considering the teratogenic potential of the newer antiepileptic drugs, three points from experience with the traditional therapies are worth making. First, even today, the full range of the teratogenicity has not been established. Second, the risk of even major malformations was not noticed until the drugs had been in extensive use for decades. Third, negative animal results are not a reliable indicator of safety. Any claims of safety for newer drugs should be taken in this context. Reported defects in infants born to mothers taking vigabatrin include spina bifida, cleft palate and absent diaphragm; conjoined twins have also been reported. Topiramate, in animal models, causes right-sided ectrodactyly and rib and vertebral abnormalities, a pattern similar to that observed with acetazolamide, also a carbonic anhydrase inhibitor. No similar human abnormalities have been reported on carbonic anhydrase inhibitors, and none in the small number of topiramate pregnancies. Gabapentin causes hydroureter and hydronephrosis in rabbits, but there have been no reported human pregnancy abnormalities. Lamotrigine has not been associated with any consistent animal or human abnormalities, although human experience is limited. Currently, the advice has to be to avoid the use of any of these drugs in pregnancy until more definitive advice can be given.

The effect of seizures on the pregnancy

Epilepsy has been reported, in retrospective (and therefore selected) series, to increase up to threefold the risks of various common complications. The perinatal mortality rate has been found to be twice that of the general population. No large-scale prospective investigation has been carried out, but there seems little doubt that these pregnancies require special consideration. The obstetricians may be more likely to recommend intervention and to manage the case in a distinctive manner. About 1–2% of all women with epilepsy will have tonic–clonic seizures during delivery and this can clearly complicate labour. The fetal heart rate can be dramatically slowed by a seizure, and fetal monitoring is recommended during vaginal delivery. Home birth should not generally be contemplated. Pregnancy has a random effect on seizure frequency. About one-third of women experience increased numbers of seizures, and this is especially likely in severe epilepsy. A similar number of women have fewer seizures during pregnancy.

Antiepileptic drug serum levels

Blood levels of antiepileptic drugs can fall during pregnancy, especially in the last trimester, and the fall is greatest with lamotrigine, the levels of which can change by over 50%. Thus, serum level monitoring is essential and, in patients at risk of seizures, the doses of the antiepileptic drugs – and especially lamotrigine – will often need to be increased in late pregnancy.

The effect of seizures on the fetus

This is a controversial area. Clearly, in the later stages of pregnancy, a convulsion carries the risk of trauma to the placenta or fetus, especially if the women falls. However, most debate has revolved around the postulation that seizures damage the fetus through lactic acidosis or hypoxia. The hypoxia is usually very short-lived and the placenta is a well-buffered system, and these risks seem intuitively likely to be small. Fetal asphyxia manifested by prolonged bradycardia has been recorded after maternal seizures, and one case of postictal fetal intracranial haemorrhage has been recorded. However, these are probably exceptional, and in most situations isolated seizures are harmless. There is one study which has suggested that first-trimester seizures are accompanied by a higher risk of fetal malformation than seizures at other times, although methodological issues cloud the reliability of the conclusions. Stillbirth has been recorded after a single seizure or series of seizures; this though must be very rare. Partial seizures have no known effects upon a fetus. However, status epilepticus during pregnancy results in significant maternal and infant morbidity.

Folic acid supplementation

The fetus of an epileptic women is at a greater than expected risk of a neural tube defect, particularly if the mother is taking valproate, but an association is also noted with exposure during pregnancy to other antiepileptic drugs. A recent Medical Research Council (MRC) trial of folic acid supplementation during pregnancy showed a 72% protective effect against neural tube defects in women who had conceived a fetus previously with neural tube defects, and a positive primary preventative action has also been demonstrated. Although there has been no specific study in epilepsy, it would seem reasonable for all epileptic women to be given folic acid supplementation during pregnancy, especially as many patients with epilepsy have low serum and tissue folate levels due to enhanced drug-induced hepatic metabolism. A dose of 4–5 mg/day is recommended on

an empirical basis, as lower doses may not fully restore folate levels.

The puerperium

There is still an increased risk of seizures in the puerperium, and precautions may be necessary. It is sometimes helpful to continue clobazam for a few days after delivery to cover this period. If antiepileptic drug dosage had been increased in response to falling levels during pregnancy, the dose should be returned during the first week to its previous levels; this is necessary as the pharmacokinetic changes of pregnancy are rapidly reversed in the puerperium. Drugs circulating in the mother's serum cross the placenta. If maternal antiepileptic drug levels were high, the infant may experience withdrawal symptoms (tremor, irritability, agitation, and even seizures) and neonatal serum levels should be measured in cases at risk.

Breast feeding

The concentration of most antiepileptic drugs in breast milk is less than 30% than that of plasma; exceptions are concentrations of ethosuximide, gabapentin, lamotrigine, levetiracetam, phenobarbital and topiramate. Furthermore, even if a drug is present in significant concentrations in breast milk, the amount ingested by the infant is usually much less than would normally be considered needed for clinical effects – and only in the case of ethosuximide, lamotrigine and phenobarbital (and primidone) are significant doses absorbed. Thus, only with these drugs are precautions necessary (and possibly levetiracetam – although data are sparse), at least at normal doses. The problem of lamotrigine is compounded if co-medication with valproate is given, which prolongs the half-life of the drug. Particular caution is advised in the case of maternal phenobarbital ingestion, as in neonates the half-life of phenobarbital is long (up to 300 h) and the free fraction is higher than in adults; neonatal levels can therefore sometimes exceed maternal levels. Neonatal phenytoin and valproate half-lives are also increased (Table 11.8). Neonatal lethargy, irritability and feeding difficulties have also been attributed to maternal antiepileptic drug intake, although evidence is slight and these findings are not correlated with maternal drug dosage or serum level.

Table 11.8 Pharmacokinetic parameters of drugs transmitted to the fetus in breast milk.

	Dose of antiepileptic drugs acquired from breast milk[a] (%)	Breast milk/ plasma concentration ratio	Elimination half-life (h)	
			Adult	Neonate
Carbamazepine	<5	0.3–0.4	5–26	8–28
Ethosuximide	>50	0.9	30–60	40
Lamotrigine	>50	0.6	12–60	Not known
Phenobarbital	>50	0.4–0.6	75–120	45–300
Phenytoin	<5	0.2–0.4	7–42	15–100
Valproate	<5	0.01	12–17	30–60

Personal communication from Dr M. O'Brien.

[a] Amount of drug received in a fully breast-fed infant – expressed as a percentage of the lowest recommended daily therapeutic dose for an infant.

Maternal epilepsy

A mother at risk from seizures with altered consciousness should not be left alone with a small child. There is a danger of dropping the child or leaving the child unattended, and maternal epilepsy probably poses a greater risk to infants and toddlers than to the fetus. Sensible precautions should be taken if seizures pose a risk of dropping a child. These might include avoiding carrying the child unaccompanied, changing and feeding the infant at ground level, and bathing the infant only when someone else is present.

Acknowledgement

This text borrowed heavily, with permission, from the *Handbook of Epilepsy Treatment* [30].

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12 Management of Epilepsy in Remission

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Introduction

Long-term outcome studies have shown that at least two-thirds of patients with newly diagnosed epilepsy will become seizure free upon antiepileptic drug (AED) treatment [1], and most patients do so immediately or shortly after beginning therapy [2]. For suitable candidates with medically refractory epilepsy, depending on the type of procedures, 50–80% may become seizure free after epilepsy surgery [3–5]. For such patients whose epilepsy is regarded as having entered 'remission', one of the key management issues concerns whether AED therapy should be continued or withdrawn. The practical dilemma arises from our inadequate understanding of the way in which AED treatment may (or may not) interact with the natural history of epilepsy [6]. For instance, it remains unclear to what extent patients with a significant period without seizures are now 'cured' (i.e. their seizure freedom is no longer dependent on treatment) of the condition, or the epilepsy is only controlled by ongoing treatment. If some are indeed 'cured' it is difficult to determine whether this is due to the treatment they received, or simply reflects the natural history of the condition ('spontaneous' remission) [6].

In practice, the decision to continue or withdraw AED therapy in these patients should involve a careful risk–benefit assessment of both seizures and continuing treatment for the individual patients. In particular, the following questions should be considered:

- What is the risk of seizure relapse upon AED withdrawal, and what are the factors associated with increased risk?
- What are the potential harmful consequences of seizure relapse?
- What are the risks in continuing AED treatment (or in other words, the benefits of AED withdrawal)?

This chapter aims to review the evidence base addressing these and other related questions pertinent to deciding whether AED therapy should be continued in a seizure-free patient, as well as to provide practical recommendations for the drug withdrawal process. The discussion will focus on drug withdrawal for patients who have become seizure free on AED treatment. Withdrawal of AEDs in patients entering remission following epilepsy surgery will also be briefly discussed.

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Risk of relapse upon AED withdrawal

Medical Research Council Antiepileptic Drug Withdrawal Study

The Medical Research Council (MRC) Antiepileptic Drug Withdrawal Study, conducted in the 1980s in the UK, remains the only large-scale randomized controlled trial that compared the policies of continued versus slow discontinuation (over 6 months) of treatment in patients who had become seizure free while on AED therapy [7]. One thousand and thirteen patients (mainly adults) who had been seizure free for at least 2 years were randomized to one of these policies, and followed up for between 1 and 5 years. Based on actuarial analysis, by 2 years after randomization, 22% of patients in the continued therapy group had relapse of seizure(s), compared with 41% in the withdrawal group. In the slow withdrawal group, 48% seizures occurred during the tapering phase.

The study was limited by its open-label design, and hence full compliance with the randomized policies was not attained and complete discontinuation was achieved in only 73% patients in the slow withdrawal group, and 35% patients randomized to continued therapy nonetheless reduced or withdrew treatment during follow-up. In addition, there was substantial self-selection with 776 eligible subjects refusing to be randomized, the most important reason being possession of a driving licence. Despite these limitations, the study remains the most authoritative trial to date comparing AED withdrawal and discontinuation in seizure-free patients.

Akershus double-blind antiepileptic drug withdrawal study

Lossius and colleagues [8] reported the first double-blind AED withdrawal study. One hundred and sixty adult patients who had been seizure free for at least 2 years on AED monotherapy were randomized to either gradual withdrawal of medication (over 3 months) or non-withdrawal. The reduced medication was replaced by a placebo to keep the study double-blinded. By 1 year, only 15% of patients in whom AED treatment was withdrawn had a seizure relapse, compared with 7% of patients in whom treatment was continued. The difference was not significant statistically. At termination of the 1-year double-blind period, most of the patients in the initial non-withdrawal group decided to taper their AEDs too. Thus, among the combined group of patients who tapered their AEDs with a median follow-up of 41 months off medication, there was a declining monthly risk of seizures from 0.01 immediately after tapering

to 0.009 at 6 and 12 months, 0.006 at 24 months and 0.003 at 36 months.

Such relapse rates were markedly lower than those observed in the MRC AED Withdrawal Study. The authors attributed the differences to inclusion of patients with perhaps 'milder' epilepsy controlled on a single AED, 67% of whom had been seizure free for more than 5 years. Normal neurological examination and use of carbamazepine prior to withdrawal were the only factors found to be associated with seizure freedom after AED withdrawal, but the ability of the study to identify other predictors was limited by its small sample size.

Non-randomized controlled or uncontrolled studies

A number of retrospective and prospective non-randomized studies, including both paediatric and adult patient populations, have examined seizure relapse rate following AED withdrawal. Using specific methodological criteria, Berg and Shinnar [9] systematically reviewed 25 reports and concluded that the typical estimate of risk of relapse was 25% at 1 year after initiating AED withdrawal and 29% at 2 years. Of all recurrences, 80% occur within the first year and 90% within the first 2 years. However, these studies likely suffered from significant selection bias and might have underestimated (or overestimated in some cases) the relapse rates, as many were small scale and retrospective and all but one were uncontrolled.

Subsequent to this review, a further controlled non-randomized study reported relapse rates in 330 patients who were referred to an epilepsy centre seizure free for at least 2 years while on stable AED monotherapy. AED discontinuation was 'proposed' to all eligible patients, of whom 225 opted to continue and 105 opted to withdraw treatment. The regimen of withdrawal was not standardized. Compliance was not reported and the mean follow-up period was nearly 4 years. Overall, 28% of patients in whom treatment was continued had a relapse, compared with 50% of patients in whom AED was withdrawn. Factors influencing the risk of seizure relapse in the multivariate model included drug withdrawal, duration of active disease, number of years of remission at study entry, abnormal psychiatric examination and epilepsy syndrome [10].

In summary, regardless of design, the comparative studies suggest that, among patients who have been seizure free on medical treatment for 2 years or more, slow AED withdrawal is associated with an approximately twofold increase in risk of relapse compared with treatment continuation. The risk is highest within the first 6–12 months of withdrawal (including the tapering phase). The actual relapse rates observed appeared to be heavily influenced by the characteristics of the populations included. It should also be noted that the stipulation of 2 years' seizure freedom before drug withdrawal is, in fact, largely arbitrary.

Early versus late withdrawal in children

Whether AED treatment can be withdrawn in patients with shorter periods of seizure freedom is particularly relevant in children when considering the potential deleterious effects of AEDs on the maturing brain. A Cochrane review in 2001 quantified seizure relapse risk after early (less than two seizure-free years) versus late (more than two seizure-free years) AED withdrawal in paediatric epilepsy patients (the reviewers could not identify any eligible trial performed in adults) [11]. Seven controlled trials, including 924 randomized children, were reviewed. The relative risk for seizure relapse in early versus late AED withdrawal was 1.32. The number needed to harm by early withdrawal was 10, meaning that for every 10 children that are withdrawn later, one seizure relapse is prevented compared with early withdrawal. There was a trend that early withdrawal was associated with greater risk of relapse in children with partial seizures or abnormal electroencephalograms (EEGs) but the association did not reach statistical significance. The systematic reviewers concluded that current evidence supported the recommendation of waiting for two or more seizure-free years before discontinuing AEDs in children, particularly if they have an abnormal EEG and partial seizures.

Rapid versus slow withdrawal

A recent Cochrane review examined the effect of the mode of AED withdrawal (whether rapid or slow tapering) on recurrence [12]. Rapid tapering was defined as withdrawal over 3 months or less and slow tapering as withdrawal over more than 3 months. Only a single study of paediatric patients was identified [13]. The rapid taper group (tapering over 6 weeks) recruited 81 participants and the slow taper group (9 months) included 68 participants. There was no significant difference in risk of relapse between the two groups. However, because of the small sample size, the reviewers felt it not possible to draw a reliable conclusion.

Factors associated with seizure relapse after AED withdrawal

A number of clinical factors have been identified that are associated with the risk of relapse following AED withdrawal in a patient who has become seizure free on AED treatment (Table 12.1). Some of these factors are discussed in detail below.

Table 12.1 Some factors that have been reported to adversely affect the risk of seizure relapse after discontinuation of AED therapy in patients with epilepsy in remission.

Short duration of seizure freedom prior to drug withdrawal
Age above 16 years
Epilepsy with onset in adolescence or adulthood
Juvenile myoclonic epilepsy
Remote symptomatic epilepsy
History of myoclonic seizures
History of multiple seizure types
History of primary or secondarily generalized tonic–clonic seizures
History of atypical febrile seizures (in children)
Prolonged period before achieving seizure control
Seizures while on treatment
Seizure control requiring multiple drug therapy
Abnormal EEG
Learning disability
Associated neurological handicaps
Previous failed attempts to stop medication

AED, antiepileptic drug.

Syndromic classification

The risk of relapsing after treatment withdrawal appears to be strongly influenced by the underlying epilepsy syndrome. Among the idiopathic epilepsy syndromes, benign epilepsy with centrotemporal spikes has an excellent long-term prognosis, and relapse is rare when medications are stopped [14]. Childhood absence epilepsy has a less certain prognosis for remission. Although, in the short term, most of these children become seizure free on treatment, about 25% relapse when medications are withdrawn [15,16]. Juvenile myoclonic epilepsy (JME) has an excellent response to treatment, but relapses are believed to occur in most patients when medications are stopped [17], although this has not been subject to rigorous study.

Remote symptomatic epilepsies are less likely to be controlled than idiopathic epilepsies [1], and are about 50% more likely to relapse if medication is stopped, according to a meta-analysis of non-randomized studies [9]. Learning disability, at least in children, may be a stronger predictor of relapse than motor impairments or other neurological disorders that are not associated with impairment of cognitive function [18]. Among the randomized trials, the impact of a remote symptomatic aetiology on risk of relapse was not clearly defined in the MRC AED Withdrawal Study [7]. This was probably related to the limited availability of sophisticated neuroimaging techniques at the time the study was conducted in the early 1980s. Findings were also conflicting in the more recent Akershus study in which all patients underwent brain MRI at recruitment [8]. Neither partial seizures nor MRI findings were associated with seizure relapse after AED withdrawal, but a normal neurological examination was a significant predictor for remaining seizure free.

Seizure type

Many studies have examined the outcome of particular types of seizures rather than syndromes. This is partly because epilepsy syndromes may be difficult to identify with confidence in patients with mild epilepsies characterized by only a few seizures responding immediately to treatment, as well as the limited neuroimaging techniques available in the older studies. The MRC AED Withdrawal Study found that a history of primary or secondarily generalized tonic–clonic seizures and myoclonic seizures was associated with increased risk of recurrence [7]. However, because a particular seizure type may be a characteristic of very differing syndromes, the results of such analyses could be conflicting. Thus, tonic–clonic seizures may occur in juvenile myoclonic epilepsy, benign epilepsy with centrotemporal spikes, juvenile absence epilepsy and many other syndromes. Similarly, simple partial seizures occur in both benign epilepsy with centrotemporal spikes and the more refractory types of temporal lobe epilepsy. Having multiple as opposed to single seizure types has been associated with a higher risk of relapse in some studies but not in others [19]; however, as severe epilepsy syndromes are often characterized by multiple seizure types, it is likely that the underlying epilepsy syndrome may better account for the likelihood of relapse after stopping AED.

Age at onset

Most studies find a favourable prognosis in epilepsy with onset in childhood, which is probably due to the occurrence of many benign epilepsy syndromes in this age group. Studies including both childhood- and adolescent-onset epilepsy usually find a substantially increased risk of relapse in those with adolescent onset. Childhood onset of epilepsy is usually associated with a risk of relapse of approximately 20% compared with 35–40% for adolescent-onset epilepsy. Adult-onset epilepsy, on the other hand, is about 30% more likely to relapse than childhood-onset epilepsy [9].

EEG findings

The value of the EEG in predicting the prognosis for relapse after stopping treatment remains controversial. Studies varied in the timing of EEG in relation to AED withdrawal and the types of abnormalities examined. Some studies have examined the degree of 'improvement' in the EEG from starting treatment to the time of its withdrawal. Most studies investigated the correlation between EEG findings immediately prior to withdrawal and relapse rate. The appearance or worsening of EEG abnormalities during the AED discontinuation period has also been suggested as a separate prognostic factor. In addition, studies varied in their focus on the types of EEG abnormalities. In one study, children with normal EEGs had an extremely low risk of relapse, those with either epileptiform abnormalities or slowing had a moderate risk and those with both epileptiform abnormalities and slowing had almost a 100% risk of relapse [20]. High rates of relapse have been reported in patients with photoconvulsive responses on EEGs [21]. In the MRC AED Withdrawal Study [7], which included mainly adult patients, an 'abnormal' (not further defined) EEG was associated with a trend towards an increase in risk of relapse. In the Akershus study, in which electroencephalography was performed routinely at baseline and during follow-up, abnormalities were categorized into epileptiform activity, focal epileptiform activity, generalized epileptiform activity and abnormal activity other than epileptiform discharges. None of the various types of abnormal EEG findings at baseline and upon retesting was associated with seizure relapse among both the withdrawal and non-withdrawal groups [8].

Overall, data suggest that electroencephalography is of greater prognostic significance in children than in adults. It is uncertain to what degree EEG abnormalities are independent prognostic variables or are simply more common in individuals already identified as high risk by clinical factors such as having symptomatic epilepsy or other adverse clinical prognostic factors [22].

Severity of epilepsy and duration of seizure freedom

A number of clinical features that may reflect the severity of epilepsy have been studied for their association with relapse after drug withdrawal. They include a history of status epilepticus, the duration of epilepsy, the number of seizures before remission, the duration of treatment, the requirement for two or more AEDs for remission and previously failed attempts to stop medication. Most studies indicate that these surrogate measures of severity all adversely affect the risk of recurrence [19]. However, no single indicator or set of indicators is clearly superior to the others as a marker of prognosis after stopping AED.

In the MRC AED Withdrawal Study, longer periods of seizure freedom (reducing the risk) and taking more than one AED

(increasing the risk) were two of the most important factors predicting relapse [7]. The duration of epilepsy and the duration of treatment are clearly correlated. There is a consensus that patients with fewer seizures, responding more rapidly to treatment, have a better outcome when medication is withdrawn. In the MRC AED Withdrawal Study, having seizures whilst on drug treatment was associated with an increased risk of relapse [7]. In both children [18] and adults [7] a previously failed attempt to stop treatment has not been found to be independently associated with an increased risk of relapse, although the power of these studies to detect an effect is poor, given that many patients might be reluctant to undertake a second attempt of withdrawal.

Although patients with status epilepticus may have poorer response to drug treatment, at least among children [23,24], those who become seizure free do not seem to have a higher risk of relapse. This was the case in both adults [7] and children [18].

Influence of individual drugs

It is often suggested that the risk of seizure recurrence may differ depending on the drug that is to be withdrawn. Withdrawal seizures are particularly said to occur with the discontinuation of benzodiazepines and phenobarbital. This idea has rarely been exposed to systematic study. There were large subgroups of patients receiving monotherapy with carbamazepine, valproate, phenytoin and barbiturate drugs (phenobarbital and primidone) in the MRC AED Withdrawal Study [7]. The temporal pattern of seizure recurrence was similar in the barbiturate group and the other groups. Perhaps surprisingly, the withdrawal of carbamazepine was associated with a lower relative risk of seizure recurrence on withdrawal than were other drugs even after adjustment for other predictors of outcome [25]. This finding has been replicated in the more recent Akershus study, in which withdrawal of carbamazepine was associated with lower risk of relapse compared with withdrawal of other AEDs [8]. The reason for this association is unclear. There is no clinical evidence to suggest that carbamazepine (or any other AED) influences the natural history of epilepsy. Since carbamazepine is the first-line treatment in partial epilepsy, investigators of the Akershus study postulated that patients demonstrating a good response to carbamazepine might have 'easy-to-treat' epilepsy [8].

Models for prediction of relapse

A predictive model for relapse in patients continuing or stopping their medication has been developed based on results of the MRC AED Withdrawal Study [26]. The model gave decreasing weight to the following factors: whether or not treatment was withdrawn, period of time that was seizure free, taking two or more AEDs, being 16 years or older at the time of withdrawal, having myoclonic seizures, having tonic–clonic seizures of any type and an abnormal EEG (Table 12.2). Comparatively simpler models have also been developed to predict relapse in children based on smaller study populations [18,27]. Scores were assigned to various predictive factors such as sex, age at seizure onset, presence of neurological abnormality, seizure types, broad epilepsy types, family history of epilepsy, EEG changes and mental retardation. The clinical usefulness of such models remains uncertain because they have not been prospectively validated in external cohorts. The model based on the MRC AED Withdrawal Study does not include the underlying syndromic classification and aetiologies of epilepsy, which is recognized to be one of the major prognostic factors of treatment outcome [28].

Table 12.2 Factors for the calculation of a prognostic index for seizure recurrence by 1 and 2 years following continued treatment or slow withdrawal of AED, in patients with a minimum remission of seizures lasting for 2 years while on treatment.

Starting score for all patients	**–175**	
Factor to be added to starting score		
Age > 16 years	45	
Taking more than one AED	50	
Seizures occurring after the start of treatment	35	
History of any tonic–clonic seizure (generalized or partial in onset)	35	
History of myoclonic seizures	50	
EEG while in remission		
Not done	15	
Abnormal	20	
Duration of seizure free period (years) = *D*	200/*D*	
Total score	*T*	
Exponentiate T/100 ($Z = e^{T/100}$)	*Z*	
Probability of seizure recurrence	*By 1 year*	*By 2 years*
On continued treatment	$1–0.89^Z$	$1–0.79^Z$
On slow withdrawal of treatment	$1–0.69^Z$	$1–0.60^Z$

D, duration of seizure-free period (years); *T*, total score; *Z*, exponentiate *T*/100 ($Z = e^{T/100}$).

Antiepileptic drug withdrawal after epilepsy surgery

Compared with the large body of literature on treatment withdrawal in patients treated medically, there is a dearth of information about the pharmacological management in postsurgical seizure-free patients. Little is known to guide whether and when AEDs should be withdrawn, or about the risk and predictors of relapse following withdrawal. There has been no randomized controlled trial to examine these issues, and only few studies have reported clinical experience from individual centres in patients undergoing a mixture of surgical procedures.

Schmidt and colleagues [29] reviewed five studies reporting relapse following planned discontinuation of AEDs in patients becoming seizure free after surgery. All were retrospective in nature. In the four adult series including a total of 464 patients with follow-up ranging from 1 to 6 years, 48% of patients discontinued AED treatment: the mean recurrence rate was 33.8%. In comparison, relapse rates were 7% and 17% for patients who continued AEDs at follow-up of 1 and 5 years. Among those who relapsed, more than 90% regained seizure control with reinstitution of AED therapy. Only one paediatric study published in abstract form was included in the review. Among 97 children with temporal and extratemporal epilepsy who became seizure free after surgery, 70% withdrew AEDs and the recurrence rate was 16%. Predictive factors of recurrence were not systematically examined in these studies.

Subsequent to this review, McIntosh *et al.* [30] reported retrospective analysis of seizure outcome in 157 patients who had been

seizure free for at least 2 years post surgery. There was no significant difference in probabilities of remaining seizure free between patients who discontinued ($n = 83$) and continued ($n = 74$) AED treatment. However, interpretation was confounded by the fact that, for those patients who continued AEDs and experienced seizure recurrence, 42% had reduced AED dosage. Another large controlled prospective study (the US Multicenter Study of Epilepsy Surgery) examined recurrence in 301 patients who had been seizure free for 1 year post surgery [31]. AEDs were reduced in 162 patients, but the proportion of patients actually achieving complete AED discontinuation was not specified. After initial reduction of AEDs, the probability of remaining seizure free was 0.84 and 0.74 at 1 and 2 years, respectively. Two-thirds of patients who relapsed after AED reduction had regained remission at the time of analysis. Relapse was significantly associated with delayed rather than immediate remission, but not with AED reduction. Of note, those who chose to continue AED regimens were also more likely to have had delayed remission, indicating selection bias. Other recent retrospective uncontrolled studies in adults [32–34] and children [35] have not shown substantially different findings.

In summary, these observations suggest that relapse upon AED reduction/withdrawal occurs in up to one-third of patients who have been seizure free for 1–2 years post surgery. The majority of these patients can expect to regain seizure control on resumption of AED treatment. There is no evidence to suggest that delaying AED withdrawal beyond 1 to 2 years of complete postoperative seizure freedom would reduce relapse rate. However, firm conclusion cannot be drawn from these mostly retrospective, non-randomized, open and often uncontrolled studies due to likely selection bias, incomplete follow-up, non-standardized AED taper regimen and sometimes confusion between reduction and complete discontinuation of AEDs in reporting.

Consequences of relapse

The potential consequences, including physical, psychological and social, of seizure relapse should be carefully considered and thoroughly discussed with the patient and family when deciding whether AED therapy should be withdrawn. Physical consequences of seizure relapse may entail accidental injuries, burns, fractures or even death. Perhaps surprisingly, these consequences have rarely been documented in the AED withdrawal studies. In the Akershus randomized controlled trial, seizures that relapsed during the 12-month double-blind study period did not cause any serious harm; however, among the 136 patients who eventually withdrew/tapered their AED therapy in the open-label extension phase, two patients apparently died of sudden unexpected death in epilepsy. Of these, one died only a few weeks after withdrawal and one died 4 years after withdrawal [8]. However, it is unknown whether continuation of AED in these two patients would have prevented their death (or indeed seizure recurrence).

Seizure relapse may induce much anxiety and affect self-esteem in the patient who might have considered himself or herself 'cured' after an initial period of seizure freedom while off medication. In addition, patients may be worried about the prognosis on resuming treatment.

Most evidence indicates that the majority of patients who relapse when medication is stopped will regain acceptable control when treatment is reintroduced. However, it is important to bear in mind that, for some patients, regaining remission may require intensive drug manipulation and may take some time, during which seizure recurrence can have serious consequences with negative impact on the patients' quality of life. In the MRC AED Withdrawal Study, 95% of those who relapsed experienced at least a 1-year remission within 3 years of the initial relapse. By 5 years, 90% had experienced a remission of at least 2 years' duration. Factors associated with a poorer outcome after relapse were having a partial seizure at the time of relapse, having a previous history of seizures while on medication and shorter duration of seizure freedom prior to the relapse [36].

Seizure relapse may have social consequences such as impact on employment and driving. In many countries, not having had a daytime seizure for certain length of time will qualify for reinstatement of driving licence, and seizure relapse may lead to loss of this privilege. Indeed in the MRC AED Withdrawal Study, possession of a driving licence was the most important reason for eligible patients to refuse randomization [7]. Therefore, an individualized approach is needed to assess the potential impact of relapse based on the patient's occupation, living conditions and caring issues. Arrangement should be made to ensure the safety of patients during and after the period of AED discontinuation whenever possible.

Risks associated with continuing AEDs (or benefits of withdrawal)

Antiepileptic drugs are associated with a range of adverse effects. Withdrawal may lead to cessation of adverse effects that the patient is experiencing at present, particularly neurocognitive side-effects, as well as avoidance of complications associated with long-term use. In the double-blind Akershus study involving adult patients taking monotherapy, AED withdrawal was associated with significant improvement in the scores of a range of neuropsychological tests, including memory, attention, psychomotor speed and executive functions [8]. Previous studies in children have demonstrated subtle improvement in cognitive symptoms and functions after AED withdrawal [37]. However, quantifying the degree to which AEDs contribute to perceived change in cognition and behaviour is often difficult because other factors, such as seizure burden and the underlying neuropathology, may also have negative effects on neuropsychological functioning [38].

Changes in other aspects of psychosocial functioning and overall quality of life associated with AED withdrawal have not been well studied. For some patients, the responsibility of remembering to take medication on time and obtaining repeat prescriptions is an unwanted source of stress. For many patients, continued therapy, with or without seizures, implies continued epilepsy. Patients who discontinue AEDs successfully are able to think that they are free not only from recurrent seizures, but also from a diagnostic label that many believe to be stigmatizing [39]. However, measuring these improvements may be logistically difficult from a research standpoint. In the MRC AED Withdrawal Study, a self-administered questionnaire covering a range of

psychosocial measures was sent to patients 2 years after randomization. AED withdrawal was associated with non-significant improvements in the sense of well-being, self-esteem, and perceived stigma, although remaining seizure free, whether on or off medication, seemed to be more important [39]. In the Akershus study, there was no significant change in health-related quality of life scores at 4 months after completion of AED withdrawal compared with baseline [8]. The authors suggested that the double-blinded design of the study excluded one known positive effect of being off medication, namely not having to take drugs regularly, and that fear of seizure relapse due to patients being blinded might even have had a negative impact on quality of life.

Successful discontinuation of AEDs means the patient is no longer exposed to the risk of complications associated with long-term treatment. One such long-term complication of increasing concern is AED-induced bone loss and resultant increased risk of fractures. Both enzyme- and non-enzyme-inducing agents are implicated, and their effects may be additive and progressive with duration of treatment [40]. Although evidence is conflicting, long-term treatment with valproate may be associated with various endocrine abnormalities including polycystic ovarian syndrome [41]. For female patients of child-bearing age, an added concern that may tip the balance towards drug withdrawal is the teratogenicity of AEDs. *In utero* exposure to the established AEDs (carbamazepine, phenobarbital, phenytoin, valproate) has been shown to increase the likelihood of fetal malformations. Among the newer drugs, recent evidence from the UK AED pregnancy registry suggests a dose–response effect for the risk of major malformation associated with lamotrigine [42]. There are insufficient data regarding the safety of other newer agents. Therefore, preconception planning is of paramount importance and AED withdrawal, if deemed appropriate, should be carried out well before the planned pregnancy.

Last but not least, since many AEDs are metabolized by and induce/inhibit the hepatic cytochrome P450 enzyme system [43], withdrawal will avoid potentially deleterious interactions with concomitant medications the patient is currently taking, or may need to take in future.

Patient attitudes

As already discussed, the decision to withdraw AED therapy will be influenced both by the risk of further seizures and by a personal view of the impact of further seizures on the individual's expectations. These issues demand careful consideration and discussion, and ultimately the decision can only be made by the patient. Personal circumstances may play a very important role. For example, a 25-year-old man whose job is dependent on holding a driving licence might well feel that a 40% risk of seizure recurrence on drug withdrawal was unacceptable. However, a similar risk in his 25-year-old wife might be acceptable if it allowed a drug-free pregnancy.

The complexity of these issues is further highlighted by studies of patients' views. Jacoby *et al.* [44] found that 43% of subjects with their epilepsy in remission were undecided what to do after a period in remission. This number was considerably reduced (to 9%) by the use of a predictive model, which presented the risk of seizure recurrence for policies of continued treatment and withdrawal. The latter policy consistently predicted greater risks of relapse than did the former. Only 10% of subjects (almost entirely adults) decided to withdraw treatment after reviewing the results of the model. In the case of children, Gordon *et al.* [45] found parents' views of acceptable risk of withdrawal corresponded very poorly with those of their physicians, and in a way that was not easily predicted by clinical factors in the children.

Clinical therapeutics

The decision to stop AED treatment in a seizure-free patient requires a careful assessment of individual risks of both seizure relapse and continuing treatment. The physician's role is to provide all necessary information for the patient and their family to make an informed decision. Generally speaking, in adults we favour continuation of treatment until there has been a remission of between 2 and 5 years, but in children shorter remission periods of 12 months may be adequate for consideration of drug withdrawal. The benefits of stopping medications in children earlier would seem to outweigh their risks in most circumstances. In adults, by contrast, the risks and consequences associated with a relapse are such that the decision to stop medications is more complicated. Overall, the clinical risks of relapse might be largely counterbalanced by the psychosocial benefits of discontinuing treatment.

In terms of the speed of withdrawal, one drug should be tapered at a time, each gradually over a 3- to 6-month period. For patients taking high dosages or multiple drug therapy, and for those taking drugs such as barbiturates and benzodiazepines, many physicians will favour a slower withdrawal. For children in remission, occasional seizures while remaining off treatment may be acceptable under some circumstances but, for many adults, a seizure recurrence will usually require the prompt reinstitution of the AED regimen that was previously successful. A wait-and-see policy might be adopted if the recurrence occurs a long time after AED therapy was withdrawn.

The patient should be counselled on any lifestyle issues that may need to be adjusted during and after drug withdrawal, considering that most relapses occur during and within the first 6–12 months after discontinuation. In the UK, the Driver and Vehicle Licensing Agency recommends that driving should cease during the period of AED withdrawal and for 6 months afterwards. We also advise women of child-bearing age to postpone pregnancy beyond the same period of time.

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13 Management of Epilepsy in Infants

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Infancy is defined as the age range that occurs between the neonatal period (the first month of life) and childhood (from 2 years of age). As in the other age ranges, the choice of antiepileptic drugs (AEDs) is highly dependent on the type of epilepsy syndrome and limited by tolerability. However, because of various age-related characteristics, management of epilepsy is quite specific in infancy.

Infancy-specific issues in the management of epilepsy

Age-dependent pharmacokinetics and pharmacodynamics

The pharmacokinetics of AEDs varies according to maturational stage. Specific pharmacokinetic features in infants compared with children and adults may include slower gastrointestinal absorption rates, higher volumes of distribution, higher apparent clearance values and shorter half-lives [1]. As a result, dose requirements need to be higher in infants than in older children and the intervals between doses need to be shortened. Equally important, intra- and interindividual variability in pharmacokinetics and dose requirement are more marked in infants than in older children.

Pharmacokinetic parameters in infants are known for most established AEDs. Valproic acid and phenobarbital exhibit relatively favourable pharmacokinetics, whereas carbamazepine and phenytoin do not. Carbamazepine daily dosages in infants need to be increased up to mean values of 30–50 mg/kg compared with 15–25 mg/kg for older children; in infants, three times daily administration is usually required although, in older age groups, two times daily dosing may be feasible. The use of phenytoin is even more problematic because of non-linear pharmacokinetics, and an adequate dose of phenytoin is particularly difficult to determine in infants [2].

As far as new AEDs are concerned, pharmacokinetic data are accruing progressively in infants. The pharmacologically active *S*(+)-enantiomer of vigabatrin has age-dependent kinetics: its absorption is significantly slower in infants than in children and adults, and its area under the curve and its elimination half-life increase linearly with age [3]. For lamotrigine, apparent clearance also increases during the first year of life from the age of 2 months [4]. An age of less than 4 years and concomitant enzyme inducers significantly increased the clearance of topiramate in children, both factors acting independently [5,6]. By contrast, inducers do not modify the pharmacokinetics of oxcarbazepine so that the concentrations of its metabolite can be predicted in infants using the same linear population-PK model as in older children [7]. Preliminary data with levetiracetam given as single dose also disclose a more rapid clearance in infants than in older ages [8].

Tolerability profiles differ in infants compared with other age groups. The risk of hepatic failure with valproate is an obvious example. Although the overall incidence is very low (1 out of 37 000), the risk is small in adults and is greatly increased below the age of 2 years, especially in infants who have been recently started on the drug and are treated with high doses, with polytherapy and in the presence of an associated psychomotor delay. Some of these patients may suffer from an undiagnosed inherited metabolic disease decompensated by valproate, such as carnitine deficiency or Alpers' disease. The changes in acylcarnitine subspecies associated with valproate treatment in epileptic children were recently identified [9]. By contrast, in infants, phenobarbital very frequently causes behavioural side-effects that limit its use in this age group: about one-third of phenobarbital-treated children develop hyperexcitability and insomnia, and the intelligence quotient (IQ) has been reported to be significantly reduced in children who received 2 years of treatment with phenobarbital as prophylaxis against recurrence of febrile seizures [10]. As far as phenytoin is concerned, overdosing is not an uncommon cause of side-effects in infants [2]. Benzodiazepines induce a paradoxical hyperexcitation, with sleep disorders rather than somnolence, in infants. When infantile spasms are treated with clonazepam, more than half of the infants experience severe side-effects, such as increased secretion of saliva, difficulty in swallowing and mucous obstruction of the bronchi. With nitrazepam, a mortality rate of 25% among infants with spasms has been reported after administration of doses above 0.8 mg/kg/day. Hypotonia and somnolence have been specifically reported in infants treated with vigabatrin. The risk for visual field defects due to vigabatrin is not evaluable at this age, even using electroretinography [11]. A recent study confirms that retinal toxicity is associated with duration and dose of vigabatrin therapy, and is therefore lower in children than in adults [12]. Adverse events were reported to be similar in infants and older children taking lamotrigine or oxcarbazepine as add-on therapy [13,14]. By contrast, metabolic acidosis induced by topiramate may be more frequent in infants than in adults [15].

Available formulations of many AEDs are unsatisfactory for use in infants. For instance, phenytoin and clobazam do not have

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a formulation suitable for infants. However, the pharmaceutical industry is currently investing in the development of formulations of new AEDs that would be appropriate for use in infants. These include liquid forms of oxcarbazepine and levetiracetam, low-dosage tablets or capsules of lamotrigine, topiramate and gabapentin, and the innovative chronosphere formulation of valproate as controlled-release formulation suitable for low daily dosages.

Characteristics of infantile epilepsies

The distinction between partial and generalized epilepsies, which is considered crucial to determine drug choice in children and adults, is not easily applicable to infants. Generalized epilepsy syndromes may be difficult to identify at onset because their initial manifestations involve partial features. There can also be rapid changes in epilepsy syndromes during infancy, eventually sometimes mixing the characteristics of both partial and generalized epilepsy, as in the case of infantile spasms progressing to partial epilepsy.

The incidence of epilepsy is higher in infancy than in childhood, possibly due to active maturational phenomena, and infancy is therefore a critical period for epileptogenesis. For the same reasons, epilepsy carries major associated risks in this age group, including a risk for altered motor function, as in the hemiplegia–hemiconvulsion syndrome, and a risk for cognitive deterioration, as in epileptic encephalopathies. Epileptic encephalopathies are conditions in which neurological deterioration results mainly from epileptic activity. Cognitive deterioration can be due to very frequent or severe seizures, or to subcontinuous paroxysmal 'interictal' activity. The former situation is seen mainly in severe myoclonic epilepsy in infancy and in migrating partial epilepsy in infancy. Cognitive deterioration related to subcontinuous paroxysmal interictal activity is seen in infants with suppression bursts, as in Ohtahara's syndrome, and in infants with infantile spasms.

Effects of antiepileptic drugs on infantile epilepsies

The efficacy of AEDs is partly determined by the type of epilepsy syndrome. Some syndromes may be improved by certain drugs, whereas others may be worsened. For example, carbamazepine may worsen infantile spasms and myoclonic epilepsies [16], lamotrigine may worsen severe myoclonic epilepsy in infancy [17] and vigabatrin may aggravate myoclonic epilepsies.

The management of infantile epilepsy syndromes

Epileptic encephalopathies

Epileptic encephalopathies comprise a series of age-related generalized epilepsy syndromes that in infancy include, in order of decreasing frequency, infantile spasms, severe myoclonic epilepsy in infancy and myoclonic epilepsy in non-progressive encephalopathy, which mostly occur between 3 and 9 months, infantile epileptic encephalopathy with suppression bursts (Ohtahara's syndrome) and infantile epilepsy with migrating partial seizures, which occur in very young babies, at a mean age of 3 months. The last two conditions are to date so intractable that no therapeutic strategy provides seizure control. The reverse is true for infantile spasms, severe myoclonic epilepsy in infancy and myoclonic epilepsy in non-progressive encephalopathy, which, although often are highly refractory, can be improved by specific treatment algorithms.

Infantile spasms (West syndrome)

Infantile spasms (IS) usually occur between 3 and 8 months, with a peak at 4 months. Diagnosis relies on the classical triad of seizures, epileptic spasms, a specific electroencephalogram (EEG) pattern (hypsarrhythmia), and psychomotor deterioration. In fact, one of the three components may be lacking or be atypical. Spasms may be clinically subtle or even subclinical, particularly at onset of the disease or when they are incompletely controlled, thus making EEG a necessary tool to prove their complete disappearance. The spasms may be symmetrical or asymmetrical. Video recording is often required for detailed analysis because asymmetry of spasms or a focal discharge may reveal a focal cortical lesion. Psychomotor deterioration is usually rapid from the time of onset of the epilepsy. The status of psychomotor development (normal or abnormal) before onset is important to be assessed because it carries prognostic implications, with better outcome for patients without regression of eye tracking.

About 30% of children with IS have normal MRI, so-called cryptogenic/idiopathic IS. A large range of cerebral lesions can be the cause in remaining cases, including cortical malformations (such as agyria–pachygyria, hemimegalencephaly, focal cortical dysplasia or polymicrogyria), sequelae of pre-, per- or postnatal anoxic ischaemia (such as periventricular leucomalacia of premature infants, porencephaly or sequelae of subdural haematoma), infection of central nervous system (such as meningitis or encephalitis), neurocutaneous syndromes (such as tuberous sclerosis or neurofibromatosis), chromosome disorders (such as Down syndrome or mutations in *ARX*, *CDKL5* [18] or *Kir 6.2* genes) or inherited metabolic disorders (such as pyridoxine dependency, Menkes' disease or mitochondrial disease due to *NARP* mutation [19]). As a result, specific aetiological treatment (pyridoxine, surgery) is rarely possible, With advances in neuroimaging techniques, the proportion of cryptogenic cases has progressively decreased. However, subtle cortical dysplasia may still be missed by MRI unless cerebral maturation and myelination is sufficient to allow clear differentiation of the grey and white matter, which is usually after 2 years of age. The availability of functional neuroimaging using positron emission tomography (PET) of glucose utilization allows up to 95% of cases initially thought to be cryptogenic to be correctly classified as symptomatic. The majority of cases with unifocal or multifocal abnormalities on PET are believed to represent dysplastic cerebral lesions. This is of importance as about 20% of infants with these lesions on PET could be candidates for epilepsy surgery if they remain refractory to medical treatment.

The term 'idiopathic West syndrome' has been used to describe the condition in some patients who recover spontaneously following a brief period of infantile spasms. Probably less than 5% of patients with West syndrome have the truly idiopathic form.

West syndrome takes a special place among childhood epilepsies because of the severe prognosis in terms of seizure recurrence and mental development, rapid deterioration of psychomotor status at the time of onset of the epilepsy and usual resistance to

conventional AEDs. The treatment of infantile spasms should therefore have two goals: the control of both the seizures and the hypsarrhythmia. Complete cessation of spasms is a prerequisite. The two major therapeutic approaches consist in hormonal treatment [adrenocorticotropin hormone (ACTH) and steroids] and vigabatrin.

Conventional antiepileptic drugs and new antiepileptic drugs other than vigabatrin

Infantile spasms are one of the most resistant epilepsy syndromes. Conventional AEDs are usually ineffective. Most of them were tested through open trials. Valproate and clonazepam control about one-quarter and one-third of the cases, respectively, but relapse rate is very high. Nitrazepam was as effective as ACTH in a randomized study, but there were life-threatening side-effects [20]. Pyridoxine has been proposed, but was disappointing [21]. A positive response was found in 12 out of 37 infants when adding sulthiame to pyridoxine as primary therapy in a randomized double-blind placebo-controlled trial performed in Germany, a country where sulthiame is extensively used in epileptic children [21]. Initial promising reports with immunoglobulins were not confirmed in later studies. Worsening has been observed with carbamazepine use [16].

Preliminary data suggest some improvement with lamotrigine used as add-on therapy [4]. Prolonged control of spasms was found in 4 out of 11 patients with refractory infantile spasms treated with add-on topiramate at a very high dose, but none of these patients had received vigabatrin before [22]. Felbamate, zonisamide, the ketogenic diet and thyrotropin-releasing hormone may be occasionally helpful in refractory cases. The two major therapeutic approaches are hormonal treatment (ACTH or corticosteroids) and vigabatrin.

Adrenocorticotropin hormone and corticosteroids

The first and most extensively studied hormonal therapy in infantile spasms is ACTH. In the review by Dulac and Schlumberger [23], the often recommended daily dose of 40 international units (IU) (3–6 IU/kg) controlled seizures initially in about 75% of the patients. A lower dose (20 IU) was less efficacious and, because of relapse long-term response rates, higher doses of ACTH (150 IU), even though they were more efficacious initially, did not show significant differences between the 40 IU and 150 IU dosage regimens. A long duration of treatment (more than 5 months) at 40 IU/day in one series seemed to be more efficient than a duration of less than 1 month in another. Relapse rates ranged from 33% to 56%. Although relapse rates according to treatment duration were not reported, the lowest relapse rates were observed in patients receiving prolonged high-dose treatment. After a first relapse, a second course of therapy produced a 74% response rate. The incidence of cushinghoid adverse events approaches 100%. Other common adverse effects include infections, increased arterial blood pressure, gastritis and hyperexcitability. These are often reported as severe, with a mortality rate between 2% and 5%.

Oral steroids are less extensively prescribed, although they seem to be better tolerated than ACTH. For hydrocortisone, reported adverse effects rates are in the order of 17%. In a prospective, randomized, blinded study, the efficacy of prednisone (2 mg/kg/day) was inferior to that of ACTH (150 IU/day) given for 2 weeks, but no differences were found when ACTH was administered at lower doses [24,25]. There are no controlled studies comparing hydrocortisone with ACTH but a prospective study including 94 infants, treated for 2 weeks with 15 mg/kg/day hydrocortisone and given tetracosactrin for another 2 weeks if spasms persisted, showed that 74% of patients benefited from low doses of oral steroids, with a relapse rate of 18%. Among the 10 infants treated secondarily with tetracosactrin, nine ceased having spasms [23]. The superiority of ACTH over oral steroids in the management of infantile spasms could be explained by its stronger feedback inhibition of corticotrophin-releasing hormone (CRH) secretion (a factor causing spasms) than that of oral steroids [26].

Rates for favourable cognitive outcome range from 14% to 58% and are higher in cryptogenic than in symptomatic cases. In a large series of 214 Finnish children with symptomatic infantile spasms, about 90 had normal intelligence and socioeconomic status at 20–35 years' follow-up [27]. They represented 64% of the surviving patients (one-third died before 3 years of age, mostly because of infection). All patients in this report had received ACTH. This argues strongly in favour of the prescription of this form of treatment, even in symptomatic cases.

Vigabatrin

The development of vigabatrin has totally modified the approach to the treatment of infantile spasms in the last 15 years. Shortly after an initial add-on open study had shown a complete control of spasms in 43% of 70 patients with refractory West syndrome [28], vigabatrin was advocated for first-line monotherapy. Because it provided an improvement over steroids or ACTH in terms of tolerability and rapidity of the effect, it rapidly became the drug of first choice for infantile spasms in most countries in which this drug was approved, and extensive experience in routine clinical practice appeared to confirm its efficacy as first-line treatment [29,30]. However, the discovery of the risk of retinal toxicity has limited enthusiasm for the use of vigabatrin.

Overall, five randomized studies have been reported of vigabatrin as first-line monotherapy in infantile spasms. In cases of spasms owing to tuberous sclerosis, vigabatrin has proved to be more efficacious, to act more rapidly and to produce less side-effects than oral hydrocortisone. In one study, a small sample of 22 patients was enough to demonstrate a difference ($P < 0.01$) between the two arms, with 100% responders on vigabatrin versus 45% on hydrocortisone at 1-month therapy [31]. In contrast, hormonal treatment was superior to vigabatrin when patients with all aetiologies of spasms were considered [32] or those with tuberous sclerosis were excluded. In a study of 107 patients, there were more responders at 2 weeks on prednisolone or tetracosactrin (73%) than on vigabatrin (54%) ($P < 0.04$) [33]. Similarly, a study of 40 infants with infantile spasms not due to tuberous sclerosis just failed to demonstrate a significant superiority of vigabatrin over placebo, with 35% and 10% responders, respectively ($P < 0.06$) [34]. Finally, a dose-ranging study confirmed the rapid effect and the significantly higher response in tuberous sclerosis than in other aetiologies, and proved that high doses (100–150 mg/kg/day) produced the best results [35].

In the long term, the efficacy of vigabatrin is maintained in about 75% of cases, a proportion similar to that of hormonal treatment, despite the short-term superiority of the latter in non-tuberous sclerosis patients [36]. The most serious side-effect of vigabatrin is its retinal toxicity, which causes constriction of the peripheral visual field. Although this condition has always been asymptomatic in children, it seems to be relatively frequent and irreversible even after stopping the drug. Prevalence of vigabatrin-induced visual field defects is now established to be lower in children than in adults (about 20% in children compared with over 30% in adults), and this is probably because of the lower cumulative drug exposure in children [12]. No case has been found in a child who has had less than 15 months of vigabatrin exposure [37]. However, it is important to caution that it is very difficult to assess the visual field by perimetry in a child below a developmental age of 8 years, although a specific method based on visual-evoked potentials seems to be promising in infants and young children [38].

Proposals for the management of infantile spasms

Vigabatrin and hormonal therapy have a similar efficacy at 1-year follow-up, whereas the former is more effective in tuberous sclerosis and the latter in other causes in the short term. They both have side-effects, although different in potential severity. Vigabatrin induces peripheral visual field in around 20% of cases, and hormonal therapy carries a mortality rate up to 5%. There are local variations in the choice of first-line therapy for infantile spasms, and the choice depends, to an extent, on the influence of local experts [39]. The following questions need to be addressed in devising a management strategy. Does early control of spasms impact on further outcome? What should be the criteria of early control? How long should treatment with vigabatrin be continued?

The early control of spasms seems to improve psychomotor development. In infants with tuberous sclerosis, early control of seizures was found to lead to a significant improvement of cognitive functions in the following 7 years, despite the possible emergence of partial seizures [40]. Developmental quotient (DQ) significantly rose in six of the seven spasm-free patients by 10 to over 45 DQ points, and autistic behaviour disappeared in five out of the six patients who manifested such behaviour. In infants with no identified underlying aetiology, the Vineland score at 1 year was higher in those allocated hormone treatment than in those allocated vigabatrin [36]. The aetiology of infantile spasms may therefore be the major factor for the choice of first-line therapy. Although data still remain limited, there is some evidence that vigabatrin should be preferred in focal cortical dysplasia but hormonal treatment should be preferred in cryptogenic or anoxic ischaemia because of prematurity.

Although individual response to treatment is unpredictable because a sizeable proportion of spasms are difficult to treat, with some responding easily, a graded therapeutic strategy should be considered, provided this is complete within less than 1 month. The endpoint in treating this syndrome is the cessation of spasms and the disappearance of spikes on EEG. Whether vigabatrin or hormonal treatment is initiated, we recommend switching to alternative therapy no later than within 4 weeks where response has been incomplete (i.e. persisting clinical or infraclinical spasms and/or persisting multifocal spikes) at adequate dosages (i.e. at least 100 mg/kg/day for vigabatrin and 40 IU/day for ACTH). Further data are needed to determine the benefit of switching or adding such alternative therapy.

The duration of vigabatrin treatment in controlled patients should be determined by balancing the risk of visual field defects and the risk of relapse of intractable spasms [41]. No case of visual field defect has been reported in children after less than 15 months of vigabatrin exposure [37]. On the other hand, the persistence of spikes on the EEG seems to be the best predictor of relapse of spasms, particularly in infants and in the case of cerebral lesions [42]. Five infants with infantile spasms associated with Down syndrome were reported in whom vigabatrin could be stopped at the age of 15 months without relapse [43]. It seems, therefore, reasonable to stop vigabatrin monotherapy at around 2 years of age if the EEG is normal. A decision to stop therapy is less easy in children with tuberous sclerosis or focal malformations of cortical development, in whom there is a substantial risk of precipitating refractory partial epilepsy when vigabatrin is discontinued [44].

Severe myoclonic epilepsy in infancy (Dravet's syndrome)

Dravet's syndrome is a rare disease affecting 1 in 30 000 to 1 in 40 000 children. Among the severe childhood epilepsies listed in the classification of the International League Against Epilepsy (1989), it is one of the most deleterious. The first seizures occur between 2 and 9 months of age. They are tonic–clonic or clonic seizures, either generalized or affecting alternatively one side of the body, often prolonged, resulting in recurrent status epilepticus and often provoked by fever. Children typically have a normal perinatal history and initially present with normal psychomotor development, normal neurological examination and normal EEG between seizures. The pattern changes from the second year, and tonic–clonic or clonic seizures persist with the same characteristics but additional myoclonia, atypical absences, and partial seizures occur, and patients develop ataxia, hyperactivity and mental retardation. The EEG shows generalized spike–waves during sleep, and spontaneous generalized spike–waves and poly-spike–waves as well as a slowing down of the background activity.

Borderline forms were identified by Japanese authors with potential later onset, no later myoclonia, better cognitive outcome, and less pharmacoresistance [45]. These forms are relatively rare and do not differ from typical Dravet's syndrome at onset. Dravet's syndrome is thus a quite homogeneous syndrome that is relatively easily identifiable, based on electroclinical features, from 1 year of age. A score of earlier diagnosis is currently under validation in Japan [46].

Nonsense mutations (or less commonly microdeletions or duplications) of the *SCN1A* gene, which codes for the α_1-subunit of the voltage-dependent sodium channel, have been identified in up to 70% of patients with Dravet's syndrome [47]. Although identifying an *SCN1A* mutation is helpful in the diagnosis of atypical forms, the diagnosis still relies on electroclinical criteria, as no mutations are found in a quite significant proportion of patients with confirmed Dravet's syndrome, and occasional patients with other types of epilepsy can also exhibit *SCN1A* mutations [48].

Severe myoclonic epilepsy in infancy is one of the few epilepsy syndromes in which the epilepsy is refractory from its onset.

Mental prognosis is poor, with a cognitive decline from normal to severe retardation as soon as the second year of life. The age of onset of mental deterioration and its magnitude seem to be related to the frequency of seizures [49]. AEDs that impact positively on seizure activity would also be expected to affect favourably cognitive prognosis.

Most authors agree that the response to conventional AEDs is generally disappointing. Valproate and benzodiazepines may decrease the frequency and duration of afebrile convulsive seizures but their effect is modest. Some investigators associate phenobarbital, phenytoin or ethosuximide with poor outcome. Japanese authors recently reported bromide as the best compound to prevent status epilepticus in a retrospective review of 99 children with Dravet's syndrome [50]. Paradoxically, some AEDs can aggravate the seizures and should be avoided. In one study, lamotrigine induced worsening of seizures in 80% of 20 patients recruited at three epilepsy centres [17]. In a personal series of 46 patients, 67% of those who received lamotrigine experienced a worsening of seizures, as did 64% of those who received vigabatrin and 61% of those who received carbamazepine [51].

Two new drugs, stiripentol and topiramate, can be helpful in some patients. The main action of the stiripentol compound, when given as add-on therapy, is to inhibit the hepatic cytochrome P450 system, resulting in increased plasma concentration of concomitant AEDs, particularly clobazam. The efficacy and tolerability of stiripentol as add-on therapy in children with refractory epilepsy were first assessed in more than 200 patients in an open trial [52]. Of the 20 children with Dravet's syndrome included in this trial, 10 experienced a more than 50% decrease in seizure frequency when stiripentol was used in combination with valproate and clobazam. These results were confirmed in 41 children with Dravet's syndrome included in a randomized placebo-controlled trial of stiripentol at a mean dosage of 50 mg/kg/day added to valproate and clobazam [53]. Fifteen (71%) patients on stiripentol were responders for tonic–clonic seizures (including nine who became seizure free), whereas there was only one partial responder (5%) on placebo. The percentage change in seizure frequency from baseline was higher on stiripentol (–69%) than on placebo (7%) ($P < 0.0001$). Twenty-one patients had moderate side-effects (drowsiness, loss of appetite) on stiripentol compared with eight on placebo. Most of these side-effects were related to a significant increase in the plasma concentration of valproic acid, clobazam and norclobazam after adding stiripentol, and disappeared when the dose of co-medication was decreased. A comparable superiority of stiripentol on placebo as adjunctive therapy in the short term was independently replicated in a second trial using the same design. To study the long-term usefulness of stiripentol, we assessed retrospectively our cohort of 46 patients with severe myoclonic epilepsy in infancy treated with stiripentol in combination with valproate and clobazam [51]. None of the patients remained seizure free after a median follow-up of 3 years; however, the frequency and the duration of seizures was significantly reduced, as was the number of episodes of convulsive status epilepticus. Response appeared to be better in younger patients. The most frequent adverse effects were loss of appetite and loss of weight. Overall, these results suggest that stiripentol maintains its long-term efficacy, and that it should be introduced in polypharmacy as early as possible in order to prevent convulsive status epilepticus.

Topiramate has not been as extensively studied. In two open studies conducted each in 18 patients, add-on topiramate was given at maximum dosages of 6–8 mg/kg/day and 12 mg/kg/day [54,55]. After a mean 1-year follow-up, 55% of the patients from both studies experienced a more than 50% seizure decrease and three were seizure free. In no patient were seizures aggravated, and side-effects were observed in nine and four patients respectively. These were generally mild and transient and related to rapid dosage titration. Adverse effects usually attributed to valproate, such as apathy and elevated blood ammonia levels, have been recently reported in patients receiving a combination of topiramate and valproate, possibly due to an interaction between these drugs. In a retrospective study of 36 patients with Dravet's syndrome retrospectively considered unsatisfactorily controlled using stiripentol, 78% showed more than 50% reduction in the frequency of generalized tonic–clonic seizures and status epilepticus after the introduction of topiramate and 17% remained seizure free for at least 4 months. The association of stiripentol and topiramate did not induce additional side-effects and did not need any particular adaptation of dosages [56].

In conclusion, because of the remarkably stereotyped clinical manifestations at onset, diagnosing severe myoclonic epilepsy in infancy is usually feasible early in the course of the disorder. The diagnosis should be suspected in any infant experiencing recurrent prolonged seizures with only moderate fever (so-called 'complex febrile seizures') and can usually be confirmed as soon as afebrile seizures occur. We suggest the use of AED treatment as soon as a first complex febrile seizure occurs in a young infant, as well as intermittent prophylaxis with diazepam in case of fever. Because of the risk of exacerbating seizures with phenobarbital in young children, we recommend valproate as the first-choice drug in this context. The combination of clobazam and stiripentol clearly adds benefit after the first prolonged seizure or repeated seizures, by decreasing seizure duration significantly. Topiramate may also be helpful in combination with valproate and benzodiazepines. We also recommend the avoidance of carbamazepine, vigabatrin and lamotrigine, which may exacerbate the epilepsy. In some countries, notably Germany and Japan, topiramate and even bromide are used as second-line therapy.

Differential responses to AEDs in patients with severe myoclonic epilepsy in infancy could be related to the existence, in this condition, of defects affecting a sodium channel gene. This could explain why AEDs which act mainly by blocking sodium channels (carbamazepine, phenytoin and lamotrigine) do not appear to be effective and may even worsen seizures, whereas broad-spectrum AEDs like valproate, benzodiazepines and topiramate may confer some benefit [57].

Myoclonic epilepsy in non-progressive encephalopathy

Non-progressive encephalopathies are a group of conditions with various aetiologies including pre- and perinatal anoxia–ischaemia, fetopathies and chromosome abnormality syndromes such as Angelman's syndrome. Myoclonic seizures are experienced by these patients during infancy, usually very early in life. In addition to massive myoclonic manifestations, erratic myoclonic manifestations are frequent and often misdiagnosed [58]. They can be

associated with non-convulsive status epilepticus, and they may be prolonged for weeks or months before being diagnosed by EEG. As a result, patients experience psychomotor and neurological deterioration, which simulates the deterioration typical of a progressive encephalopathy. Because of the myoclonic components, carbamazepine, phenytoin and vigabatrin frequently worsen the epilepsy. Valproate is usually the first-choice agent, followed by benzodiazepines. Lamotrigine has unpredictable effects: it may be very useful in some cases and precipitate myoclonus in others. Piracetam provides benefit in Angelman's syndrome, due to its antimyoclonic effects, but the high doses required are difficult to administer to infants [58].

Symptomatic and cryptogenic partial epilepsies

Diagnosing focal seizures and focal lesions is more difficult in infants than in later life. Because of the lack of subjective feedback from the patient, focal ictal symptoms are usually missed when they do not include any motor component. Because of myelinic immaturity, focal cortical dysplasia may be undetectable on MRI. As a result, pure focal epilepsies are likely to be overlooked in infancy. Moreover, a large proportion of infants with partial seizures develop infantile spasms during the first year of life. Choice of AED should therefore take into account the potential risk of generalized spasms being facilitated by the administration of carbamazepine. Carbamazepine therapy should be avoided unless there are facilities for close follow-up of clinical signs and EEG changes, especially in the first 6 months of life when spasms frequently develop. Valproate is preferred as a first-line agent, although it is often ineffective in infants with symptomatic partial epilepsy. Phenytoin and benzodiazepines are not recommended because of unfavourable pharmacokinetic and/or safety profiles in infants [2]. Among the new AEDs, only vigabatrin is currently approved for this age range, but four others have been recently studied in randomized controlled trials as adjunctive therapy in infants with partial-onset seizures. Gabapentin was found not to demonstrate any efficacy. High doses of oxcarbazepine (60 mg/kg/day) proved to be more efficient than low doses (10 mg/kg/day) [13], and lamotrigine to be more efficient than placebo using a randomized withdrawal design [14]. Studies of levetiracetam are currently under way.

Sturge–Weber syndrome has a particular place among symptomatic partial epilepsies in infancy. The diagnosis can be made before the occurrence of the first seizure, from the facial angioma located in the first division of the trigeminal nerve and by neuroimaging. More than 75% of patients develop epilepsy, 50% of them during the first year of life. These infantile seizures often result in convulsive status epilepticus and carry great risks for motor and mental development. Therefore, preventative treatment could be started before the first seizure occurs. We compared 37 children with Sturge–Weber disease, of whom 16 were treated with phenobarbital before the occurrence of the first seizure and 21 were treated after the first seizures [59]. Although prophylactic treatment did not significantly prevent the incidence of seizures and motor deficits, it decreased the number of episodes of status epilepticus, and mental development was found to be better in the group given prophylactic treatment (44% were mentally delayed in the latter group, compared with 76% in patients started on treatment after the appearance of seizures). Although a randomized prospective study is necessary to confirm these results, Sturge–Weber disease constitutes a possible model for the study of disease modification in severe epilepsy.

Idiopathic epilepsies

Compared with catastrophic epilepsies, idiopathic (i.e. 'benign') epilepsies are rare in infants. They include benign infantile convulsions, either sporadic or familial, and benign myoclonic epilepsy in infancy. In these conditions, there is normal development prior to the onset of the seizures, there are no underlying disorders, no neurological abnormalities and the interictal EEG is normal. Seizures are easily and completely controlled by treatment, usually with valproate given in monotherapy. These patients usually show a normal developmental outcome, although some learning difficulties have been reported occasionally on long-term follow-up of patients with benign myoclonic epilepsy in infancy [60].

Initiation of treatment in infantile epilepsies

The decision to start treatment in infantile epilepsies depends to a large extent on whether the syndrome is identified, because drug choice varies depending on the syndromic form. Thus, vigabatrin is usually preferred in infantile spasms or symptomatic focal epilepsies before 6 months of age, valproate is often the first choice in generalized or focal convulsive epilepsies (including severe myoclonic epilepsy in infancy) and carbamazepine can be given in symptomatic partial epilepsies after the age of 6 months to minimize the risk of the occurrence of spasms (which is considerable in younger age groups). If the syndrome is not identified, treatment with valproate is preferred. If there is any suspicion of an inborn error of metabolism, which represents a contraindication to the use of valproate (e.g. Alpers' disease), clobazam should be considered.

The prognosis of infantile epilepsies partly depends on a timely and appropriate AED choice. Diagnosis of the epilepsy syndrome is crucial in this process, since inappropriate medication can worsen the condition. There is place for the use of some new compounds as agents of first choice in this age range.

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14 Management of Childhood Epilepsy Syndromes

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Introduction

The syndromic approach to the epilepsies has proved very useful in children. A syndrome diagnosis at presentation may be possible in as many as 77% of children [1] and it usually offers the best guide to appropriate clinical management, including antiepileptic drug (AED) treatment. The International League Against Epilepsy (ILAE) currently recognizes well over 30 epilepsy syndromes, most of which occur in children. This chapter covers treatment of epilepsy syndromes encountered after 2 years of age, including adolescence. It concentrates on syndromes that characteristically only start in this age group. It is sometimes difficult to draw boundaries. Febrile seizures often start in infancy and juvenile myoclonic epilepsy and only epilepsy with generalized tonic–clonic seizures are often not diagnosed until adult life. All three are considered here. On the other hand, some idiopathic and familial focal epilepsies, such as autosomal dominant familial frontal lobe epilepsy and symptomatic focal epilepsies, including mesial temporal lobe epilepsy, are not included, despite being common in children. This is because they are not characteristically childhood as opposed to adult conditions.

Epilepsy syndromes are traditionally classified according to whether the seizure types encountered are generalized (generalized epilepsy syndromes) or focal (focal epilepsy syndromes) and whether the cause of the epilepsy is known (symptomatic epilepsy syndromes), unknown but an underlying cause suspected (probably symptomatic epilepsy syndromes) or unknown with no underlying structural brain lesion or other neurological signs or symptoms – only epilepsy (idiopathic epilepsy syndromes). However, this classification has largely outlived its usefulness. Not all seizures can be classified as focal or generalized; some epilepsies are characterized by both focal and generalized seizures and some epilepsy syndromes exist in idiopathic, symptomatic and probably symptomatic forms. In this chapter, a pragmatic approach will be followed. Treatment of febrile seizures (the most common epileptic seizure disorder, but not usually considered a type of epilepsy) will be considered first, followed by idiopathic generalized epilepsies (IGEs) (Table 14.1), idiopathic focal epilepsies (Table 14.2) and epileptic encephalopathies (Table 14.3). For each, the evidence from randomized controlled studies will be reviewed, followed by a review of important information from open studies, case series and case studies.

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Treatment recommendations from the ILAE [2], the American Academy of Neurology (AAN) and the American Epilepsy Society [3,4] and the National Institute for Health and Clinical Excellence (NICE) [5] will be summarized. Recently surveys of the prescribing choices of expert US [6] and European physicians [7] who regularly treat children with epilepsy have been published and the findings from these are also summarized. Finally, practical advice will be given, based upon the various sources of evidence and personal experience.

Treatment of childhood epilepsy: the evidence base

The randomized controlled trial is considered the 'gold standard' when determining the effectiveness of a medical therapy. However, to be meaningful, at least two conditions must be met: the disorder being studied must be well defined with clear-cut diagnostic criteria, and the therapeutic outcome must be measurable and clinically relevant [8]. Many drug trials undertaken in childhood epilepsy fail one or both of these [9]. They often group together disparate disorders, such as focal seizures, generalized seizures or new-onset seizures, on the basis that this is necessary to achieve sufficient power. However, the STICLO study in Dravet's syndrome demonstrated that this is not always the case [10]. Many randomized controlled trials are of short duration, compare the study drug with placebo rather than with a comparator used in clinical practice and have as their principal outcome measure the proportion of children who have at least a 50% reduction in seizures compared with baseline. These studies are designed to achieve a market licence but are of little clinical relevance. The need for trials to be clinically relevant is emphasized in the ILAE's treatment guidelines [2]. The guidelines define class I evidence as that obtained from a randomized double-blind controlled trial with treatment duration of at least 48 weeks and with information on at least 24 weeks' seizure freedom data or at least 48 weeks' retention data. Moreover, there has to be demonstration of superiority or 80% power to detect at least a 20% difference in efficacy/effectiveness against a suitable comparator. No such study has been reported in any of the syndromes considered here.

Treatment of febrile seizures

Febrile seizures are the commonest epileptic disorder with a cumulative incidence of 2–5%. However, because the seizures

Table 14.1 Summary of the electroclinical features of the IGE of childhood.

Syndrome	Age at onset (years)	Seizure type(s)	Clinical notes	Principal EEG features	Prognosis
CAE	2–10 years (peaks at 5–7)	TAS: these usually last 4–20 s, are frequent (usually tens per day) with abrupt and severe impairment of consciousness (and hence frequent automatisms)	There is an important debate regarding the limits of CAE. Many authorities now favour excluding children with the following: other seizure types (except febrile) prior to onset of TAS; marked myoclonic phenomena during TAS; TAS (prior to AED treatment) with mild impairment of consciousness; irregular spike–wave discharges; photosensitivity	Regular generalized 3-Hz spike–wave discharges easily provoked by hyperventilation	Applying strict diagnostic criteria (see clinical notes), probably around 90% become seizure free by 12 years. Occasional patients develop GTCS in childhood, adolescence or adult life
JAE	5–20 years (peaks at 9–13)	TAS (all patients): these are similar to those in JAE but are not as frequent (a few per day maximum) GTCS (approx. 80% patients or more) MS (around 1 out of 5 patients) Absence status epilepticus (probably fairly common)	As for CAE there is debate as to the limits of this syndrome: Similar exclusion criteria have been proposed except that other seizure types, such as GTCS and MS, may precede TAS. GTCS often become the main problem in adolescence and adult life. MS tend to be infrequent and random rather than showing the characteristics of JME	Similar to CAE. Focal epileptiform abnormalities and abortive asymmetrical bursts of spikes/poly-spikes are common	Probably a life-long disorder, although seizures can be controlled in most patients. With time TAS usually become less frequent, shorter and associated with less severe impairment of consciousness. GTCS may become more troublesome
JME	TAS can begin as early as 5 years: more usually the syndrome begins in late childhood, adolescence or early adult life	TAS (about 1 out of 3 patients): usually brief with mild impairment of consciousness MS (all patients): characteristically occur shortly after awakening or towards the end of the day when tired. May be single or multiple, inconspicuous or violent GTCS (nearly all patients): usually start after GTCS. Often preceded by showers of MS Myoclonic and absence status epilepticus both described	Sleep deprivation, fatigue and alcohol are powerful seizure precipitants in IGE, but particularly JME. Clinical photosensitivity is less frequent than on EEG	Irregular generalized 3- to 6-Hz spike–wave discharges (poly-spikes common). Focal abnormalities with single spikes, spike–wave complexes or slow waves common Photosensitivity in 1 out of 3 patients	Probably a life-long disorder, although seizures can be controlled in most patients
EGTCS	From 6 until adult life (peak in mid-late adolescence)	GTCS	Seizures often occur shortly after awakening	Generalized spike–wave discharges. Up to 1 out of 4 of patients are photosensitive	Probably a life-long disorder, although seizures can be controlled in most patients
Jeavon's syndrome	2–14 years (peak 6–8)	Eyelid myoclonia with or without absences (all patients) GTCS (probably in all patients in the long-term) Absence status epilepticus relatively common	Seizures are provoked by eye closure (voluntary, involuntary or reflex) in light and by other photic factors. There is a controversy about the role of self-induction in the provocation of seizures	Generalized 3- to 6-Hz spike–wave discharges (mainly poly-spikes) which are brief and characteristically provoked by eye-closure in an illuminated recording room and by intermittent photic stimulation	Probably a life-long disorder and seizures (particularly eyelid myoclonia) are often very resistant to medication. However, photosensitivity often disappears in middle age
PMA	2–13 years (median 10)	TAS with rhythmic contractions of the perioral and/or jaw muscles accompanied by variable impairment of consciousness GTCS (probably all patients) Absence status epilepticus common		Generalized spike–wave discharges. Focal abnormalities common. No photosensitivity	Unclear, but may be life-long

CAE, childhood absence epilepsy; EEG, electroencephalogram; EGTCS, epilepsy with generalized tonic–clonic seizures only; GTCS, generalized tonic–clonic seizures; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; MS, myoclonic seizures; PMA, perioral myoclonia with absences; TAS, typical absence seizure.
Doose syndrome and epilepsy with myoclonic absences (EMA) are also now considered IGE. Their electroclinical features are summarized in Table 14.3.

Table 14.2 Summary of the electroclinical features of the idiopathic focal epilepsies of childhood.

Syndrome	Age at onset	Seizure types	Clinical notes	Principal EEG features	Prognosis
BECTS	1–14 years (peak 8–9 years)	Focal seizures with hemifacial sensorimotor symptoms, oro-pharyngo-laryngo manifestations, speech arrest and hypersalivation. Secondary generalized seizures are common in sleep	One of the most common epilepsy syndromes with a prevalence of 15% in children aged 1–15 years with seizures. Three out of four seizures occur in sleep, mainly at sleep onset or just before awakening. Most are short (1–3 min) and the total seizure count is usually low	The EEG hallmark is centrotemporal spikes which are high-amplitude sharp- and slow-wave complexes, localized in the C3–C4 or C5–C6 electrodes. They may be unilateral or bilateral, independently right or left. They are activated by sleep. Background EEG is normal	Remission is usually within 2–4 yeas of onset and expected before age 16 years. Some children develop cognitive, linguistic and/or behavioural abnormalities, although these are usually mild. A very small number have atypical evolutions associated with continuous spikes and waves during slow-wave sleep
PS	1–14 years (peak 4–5 years)	Autonomic seizures, particularly with emetic symptoms (nausea, retching ± vomiting). Syncopal-like episodes are also common. Consciousness is usually retained initially but becomes impaired. Secondary generalization may occur	The second most common idiopathic focal epilepsy of childhood. Two out of three of seizures start in sleep. Seizures are characteristically long, often constituting autonomic status epilepticus. The total seizure count is usually low	The interictal EEG shows great variability. Multifocal, high-amplitude, sharp- and slow-wave complexes are common. These are most often seen in the occipital regions but often affect other brain regions as well. Background EEG is normal	Remission usually occurs within 1–2 years of onset. The risk of epilepsy in adult life appears to be no higher than in the general population. As for BECTS, atypical evolutions have been described
IOLE (including IPOLE)	3–15 years. The photosensitive form may begin in childhood or adult life	Focal (occipital) seizures mainly with elementary visual hallucinations, blindness or both. Ictal or, more usually, postictal headache is common. Spread with other focal seizure symptoms or secondarily generalization occurs but relatively infrequently	A relatively rare syndrome. Seizures are usually frequent, diurnal and short (from a few seconds to 1–3 min). In the photosensitive form of the syndrome seizures are sometimes or always precipitated by photic factors	The characteristic interictal EEG abnormality is high-amplitude sharp- and slow-wave complexes occurring in long runs in the posterior head regions (occipital paroxysms). In the photosensitive form of the syndrome there is occipital and/or generalized photosensitivity	Remission occurs in 50–60% of patients within 2–4 years of onset. Persistence into adult life is not uncommon. The prognosis of the photosensitive form depends on the severity and persistence of the photosensitivity and the degree of exposure to provocative factors

BECTS: benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy); EEG, electroencephalogram; PS: Panayiotopoulos' syndrome (early-onset benign childhood occipital epilepsy – Panayiotopoulos type); IOLE: idiopathic occipital lobe epilepsy (late-onset childhood occipital epilepsy – Gastaut type); IPOLE: idiopathic photosensitive occipital lobe epilepsy.

occur in the context of a reversible disturbance in homeostasis, even if recurrent, they are not considered a manifestation of epilepsy. Onset usually occurs between 6 months and 3 years and they are recurrent in one-third of affected children. Most febrile seizures are convulsive and, if short (<15 min), generalized and not repeated in the same illness, they are classified as simple; otherwise, they are classified as complex. Complex features increase the risk of subsequent epilepsy, which overall has an incidence of 7% by 25 years. Febrile seizures are considered benign, although they are very occasionally the first manifestation of a severe epilepsy, such as Dravet's syndrome. Prolonged febrile seizures are implicated in the pathogenesis of mesial temporal sclerosis, although the nature of this relationship remains controversial.

Findings from double-blind randomized controlled studies

An influential meta-analysis found nine placebo-controlled studies reviewing the effect of prophylactic treatment with antiepileptic drugs on the recurrence rate of febrile seizures [11]. The risk was significantly lower in children receiving continuous phenobarbital or sodium valproate than in those receiving placebo. However, four patients needed to be treated with valproate and eight with phenobarbital to prevent one recurrence. Compared with placebo, regular pyridoxine and regular phenytoin were not found to prevent recurrences.

An alternative approach to prevent recurrences has been the intermittent but regular use of antiepileptic or antipyretic drugs at the time of fever. The aforementioned meta-analysis found that

Table 14.3 Summary of the electroclinical features of the epileptic encephalopathies of childhood.

Syndrome	Aetiology	Principal clinical features	Principal EEG features	Prognosis
LGS	Two out of three cases are symptomatic of a variety of diffuse, multifocal and even focal brain insults, including some metabolic disorders. Also exists in a probably symptomatic form. A true idiopathic form recognized by some authorities	Onset is from infancy to late childhood, but peaks age 3–5 years. It may develop from West syndrome. Consists of a triad of multiple seizures, characteristic EEG and learning problems. The most characteristic seizures are tonic (especially nocturnal), atonic and atypical absence seizures. Other seizures, including GTCS and focal seizures, may occur. Myoclonic seizures are not prominent. Non-convulsive status epilepticus is common	The background EEG is usually slow. Paroxysms of slow (<2.5 Hz) generalized spike–wave discharges are characteristic and may be ictal or interictal. Sleep recordings often have paroxysms of fast rhythms which may be accompanied by tonic seizures	Overall, 80–90% continue to have seizures into adult life. Severely impaired cognition, often with significant behavioural disturbances, is the rule. A good prognosis, with normal cognitive functioning is reported in around 10–15% of cases
Doose syndrome	Considered an IGE. Similar symptomatic cases occur	Onset is in early to mid-childhood and peaks at 2–4 years. Febrile and afebrile GTCS usually precede the onset of myoclonic–astatic seizures, often with atonic, myoclonic and absence seizures. Myoclonic–astatic status epilepticus is common and is associated with a poorer prognosis. Associated neuropsychological deficits vary greatly in their occurrence and severity	EEG background is usually normal at start but may deteriorate. Paroxysms of 2- to 3-Hz generalized spike–wave and/or irregular spikes or poly-spikes are characteristic. There may be photosensitivity	Variable. Around one-half eventually become seizure free with normal or near-normal development
LKS	Characteristically develops in children with no structural brain problems who were previously neurodevelopmentaly normal	Onset is usually in early/mid-childhood, peaking at 5–7 years. Consists of a triad of acquired language problems (initially a verbal auditory agnosia which may progress to a global aphasia), cognitive and behavioural abnormalities (often severe), and seizures. Seizures can be of many different types and are often infrequent	EEG is mainly characterized by posterior temporal lobe sharp- and slow-wave complexes. These are highly activated by sleep. CSWS occurs at some stage in most, but not all cases	Seizures and EEG abnormalities often remit in childhood/adolescence and this is often accompanied by improvement in the language and neuropsychological disturbances. Around one-half of those affected function reasonably normally in adult life
CSWS	Around one-half of cases are symptomatic of pre-existing brain insults. May develop in children with idiopathic focal epilepsies, including BECTS	Occurs throughout childhood. Peak age of onset is 4–5 years of age. The first stage consists of a rather non-specific epilepsy (although seizures are most often nocturnal and often consist of prolonged hemiconvulsions). Usually after 1–2 years there is a deterioration in seizure control with neuropsychological decline. An opercular syndrome is seen in some. Eventually seizures and EEG abnormalities remit with some improvement in neuropsychological functioning	Continuous spike–waves during non-REM sleep is characteristic of the second stage of the condition	After seizures remit, most patients are left with significant neuropsychological deficits, often severe
EMA	Now classified as an IGE. However, similar symptomatic cases occur	Occurs throughout childhood. Peaks at about 7 years. The characteristic clinical features are myoclonic absences which are similar to typical absences but are accompanied by rhythmic myoclonic jerks, mainly of the shoulders, arms and legs. These may be accompanied by other generalized seizure types. Cognitive and behavioural decline is seen in at least half of patients, even if development was normal prior to the onset of the myoclonic absences	EEG background usually normal at start but may deteriorate or be abnormal in symptomatic cases. Discharges similar to those in CAE accompany myoclonic absences with myoclonic jerks occurring with the spike component of spike–wave complexes	Variable, a minority of children eventually become seizure free with normal or near-normal development

BECTS, benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy); CAE, childhood absence epilepsy; CSWS, continuous spikes and waves during slow sleep; EEG, electroencephalogram; EMA, epilepsy with myoclonic absences; GTCS, generalized tonic–clonic seizures; IGE, idiopathic generalized epilepsy; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; REM, rapid eye movement.

diazepam was not effective in preventing recurrences [11]. However, a later meta-analysis found that such treatment was effective, with 11.2% of children treated with diazepam during febrile episodes having one or more recurrences compared with 17.2% treated with placebo [12]. Later studies [13,14] showed that intermittent diazepam is particularly effective in those at high risk of recurrences. Intermittent paracetamol or ibuprofen administered during febrile episodes does not prevent further febrile seizures in those at risk [15,16].

Recommendations from expert committees and concluding remarks

Despite the demonstration that prophylactic treatment, whether regularly with phenobarbital or sodium valproate or intermittently with benzodiazepines, reduces the recurrence risk of febrile seizures, clinical practice has switched decisively away from such treatment. This partly reflects the adverse effect profiles of the available agents but is also heavily influenced by the benign nature of febrile seizures. The long-term outcome, including scholastic abilities, was found to be no different in a cohort of 289 children with febrile seizures randomized to either intermittent prophylaxis during fever with diazepam or no prophylaxis [17].

The American Academy of Pediatrics concluded that neither continuous nor intermittent prophylaxis with antiepileptic drugs could be recommended and that neither could the administration of antipyretic drugs during febrile illnesses in order to prevent recurrent febrile seizures [18]. The recommendations of the US and European expert committees are shown in Table 14.4.

Febrile status, usually defined as a febrile seizure lasting at least 30 min or a series of febrile seizures over a period of at least 30 min without full recovery of consciousness between seizures, is still considered an emergency with a risk of both morbidity and mortality. Termination of prolonged febrile seizures using standard protocols for the treatment of status epilepticus is appropriate. Many paediatricians provide the carers of children judged to be at high risk of prolonged febrile seizures with 'rescue medication', particularly rectal diazepam and more recently nasal or buccal midazolam [19]. Given that most febrile seizures last less than 2 min, it is usual to advise administration of rescue medication for seizures lasting longer than this. However, provision of such medication to all children who have had febrile seizures is probably not justified.

Treatment of idiopathic generalized epilepsies

Idiopathic generalized epilepsies (IGEs) are common, particularly in mid and late childhood and adolescence. In these epilepsies, three seizure types are recognized: typical absence seizures (TAS), myoclonic seizures (MS) and generalized tonic–clonic seizures (GTCS). IGE is usually subdivided, and the best-characterized subdivisions are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME). The ILAE also recognizes benign myoclonic epilepsy of infancy (BMEI), epilepsy with generalized tonic–clonic seizures only (EGTCS), epilepsy with myoclonic absences (EMAs) and epilepsy with myoclonic–astatic seizures (Doose syndrome). BMEI usually begins under the age of 2 years and is considered in Chapter 14. EMA and Doose syndrome were, until recently, considered as probably symptomatic or symptomatic epilepsies. Both often behave as epileptic encephalopathies and are considered later in this chapter. Finally, there are other proposed syndromes of IGE that characteristically start in childhood and adolescence but are not yet recognized by the ILAE. These include eyelid myoclonia with absences (also known as Jeavon's syndrome) and perioral myoclonia with absences (PMA). Clinical and electroencephalogram (EEG) features of all these syndromes are summarized in Table 14.1.

Findings from double-blind randomized controlled trials

The evidence base from double-blind randomized controlled trials for the treatment of IGE in children is extremely poor. A recent Cochrane review of TASs in children and adolescents found four studies that met its inclusion criteria. However, serious methodological problems were identified in all studies, and a meta-analysis was not considered appropriate. The Cochrane review concluded that these studies did not reliably inform clinical practice [20]. There are no Cochrane reviews to guide management of the other IGEs.

Ethosuximide and sodium valproate have been used for many years to treat IGE. Suzuki *et al.* [21] compared ethosuximide with sodium valproate in 35 children with 'pure petit mal seizures' in a double-blind trial and found no significant difference in response. Sato *et al.* [22] also compared ethosuximide and sodium valproate in a complicated double-blind study that included assessment of efficacy in treatment-naive patients and in patients refractory to ethosuximide. There was a good response to both drugs in the treatment-naive patients but no overall evidence of the superiority of either drug either in treatment-naive patients or in refractory patients. Sato *et al.* [23] compared ethosuximide and clonazepam in 79 children with absences. The retention rate at the end of the trial was better with ethosuximide (92%) than with clonazepam (69.8%).

Frank *et al.* [24] used a complicated trial design in which children with TAS first received lamotrigine in an open-label phase. Responders were then randomized in a double-blind manner to treatment with either lamotrigine or placebo. In the open-label phase 71% of patients became seizure free. In the randomized phase 64% were seizure free on lamotrigine compared with 21% on placebo ($P = 0.02$). Beran *et al.* [25] used a cross-over design to compare lamotrigine and placebo in 22 patients with various IGE who had failed on sodium valproate. Fifty per cent of those with GTCS and 33% with absences had at least a 50% reduction in seizures with lamotrigine.

A double-blind placebo-controlled trials of the use of topiramate in children and adults with primary generalized tonic–clonic seizures was reported by Biton *et al.* [26]. Many, but not all, of the patients had IGE and a post hoc analysis of the 22 patients with JME found that topiramate reduced GTCS by 73% compared with 18% in the placebo group [27].

The efficacy of levetiracetam for the treatment of MS and GTCS in IGE in adolescents and adults has been evaluated. Verdru *et al.* reported that 58% of adolescents and adults treated with levetiracetam in a double-blind, placebo-controlled trial of 122 patients had at least a 50% reduction in seizures compared with 23% treated with placebo [28]. Berkovic *et al.* found that 72% of children and adolescents with an IGE treated with

Table 14.4 Summary of treatment recommendations made by the International League Against Epilepsy (ILAE), the National Institute for Health and Clinical Excellence (NICE) and by panels of expert US and European physicians who regularly treat children with epilepsy.

Syndrome	ILAE	NICE	US experts	European experts
Febrile seizures	No guidance given	No guidance given	*First-line preventative treatment:* no AED treatment *High second-line options:* phenobarbital *Treatment for acute treatment of prolonged febrile seizure or cluster of febrile seizures – treatment of choice:* rectal diazepam	*First-line preventative treatment:* valproate *Treatment for acute treatment of prolonged febrile seizure or cluster of febrile seizures – treatment of choice:* rectal diazepam *High second-line options:* intranasal midazolam, rectal lorazepam
CAE	*'Can be considered as initial monotherapy':*[a] ethosuximide, valproate, lamotrigine *Ineffective:* gabapentin *'May precipitate or exacerbate TAS':* carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin	*First-line:* ethosuximide, lamotrigine, valproate *Second-line:* levetiracetam, topiramate *To be avoided:* carbamazepine, oxcarbazepine, phenytoin, tiagabine, vigabatrin	*First-line treatment of choice:* ethosuximide *Other first-line therapies:* valproate, lamotrigine *High second-line options:* zonisamide, topiramate	*First-line treatment of choice: valproate* *Other first-line therapies:* lamotrigine, ethosuximide *High second-line options:* None
JAE	See above	*First-line:* lamotrigine, valproate *Second-line:* levetiracetam, topiramate *To be avoided:* carbamazepine, oxcarbazepine, phenytoin, tiagabine, vigabatrin	*First-line:* valproate, lamotrigine *High second-line options:* zonisamide, topiramate	*First-line treatment of choice:* valproate *Other first-line therapies:* lamotrigine *High second-line options:* ethosuximide
JME	*'May have some efficacy':* clonazepam, lamotrigine, levetiracetam, topiramate, valproate, zonisamide – carbamazepine, gabapentin, oxcarbazepine, phenytoin *'May precipitate or aggravate TAS and MS':* tiagabine and vigabatrin *'May exacerbate seizures in JME':* lamotrigine	*First-line:* lamotrigine, valproate *Second-line:* clobazam, clonazepam, levetiracetam, topiramate *Other drugs:* acetazolamide *To be avoided:* carbamazepine, oxcarbazepine, phenytoin, tiagabine, vigabatrin	*First-line treatments of choice:* valproate, lamotrigine (in males); lamotrigine (in females) *Other first-line therapies:* valproate (females); topiramate (males and females) *High second-line options:* zonisamide, lamotrigine	*First-line treatment of choice:* valproate (males); lamotrigine (females) *Other first-line therapies:* lamotrigine (males); valproate (females) *High second-line options:* levetiracetam (males and females)
Other IGEs	No guidance given	*For 'generalized tonic–clonic seizures only'* *First-line:* carbamazepine, lamotrigine, valproate, topiramate *Second-line:* levetiracetam *Other drugs:* acetazolamide, clobazam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, primidone *To be avoided:* tiagabine, vigabatrin	No guidance given	No guidance given
BECTS	*'Can be considered as initial monotherapy':* carbamazepine, valproate *'Potentially effective/ efficacious':* gabapentin, sulthiame *'Class IV evidence suggests that . . . some children . . . do not need AED therapy'*	*First-line:* carbamazepine, lamotrigine, oxcarbazepine, valproate *Second-line:* levetiracetam, topiramate *Other drugs:* sulthiame	*Treatments of choice:* oxcarbazepine, carbamazepine *High second-line options:* gabapentin, lamotrigine, levetiracetam	*Treatment of choice:* valproate *High second-line option:* carbamazepine
PS	No guidance given	*First-line:* carbamazepine, lamotrigine, oxcarbazepine, valproate *Second-line:* levetiracetam, topiramate	No guidance given	No guidance given
IOLE	No guidance given	*First-line:* carbamazepine, lamotrigine, oxcarbazepine, valproate *Second-line:* levetiracetam, topiramate	No guidance given	No guidance given

Table 14.4 *Continued*

Syndrome	ILAE	NICE	US experts	European experts
LGS	No guidance given	*First-line:* lamotrigine, valproate, topiramate *Second-line:* clobazam, clonazepam, ethosuximide, levetiracetam *Other drugs:* felbamate *To be avoided:* carbamazepine, oxcarbazepine	Initial monotherapy *First-line treatment of choice:* valproate *Other first-line therapies:* topiramate, lamotrigine *High second-line options:* zonisamide Second monotherapy after valproate *Treatment of choice:* topiramate *Other first-line options:* lamotrigine *High second-line options:* zonisamide, levetiracetam, ketogenic diet, felbamate Second monotherapy after topiramate *Treatment of choice:* valproate *Other first-line options:* lamotrigine *High second-line options:* zonisamide, levetiracetam Second monotherapy after lamotrigine *Treatments of choice:* topiramate, valproate *High second-line options:* zonisamide, levetiracetam, ketogenic diet	Initial monotherapy *First-line treatment of choice:* valproate *High second-line options:* lamotrigine, topiramate, CBX Second monotherapy after valproate *First-line treatment of choice:* lamotrigine *Other first-line therapies:* topiramate *High second-line options:* CBX, CZP, levetiracetam Second monotherapy after topiramate *First-line treatment of choice:* valproate *Other first-line therapies:* lamotrigine *High second-line options:* CBX Second monotherapy after lamotrigine *First-line treatment of choice:* valproate *Other first-line therapies:* topiramate *High second-line options:* CBX, levetiracetam
Doose syndrome	No guidance given	*First-line:* carbamazepine, clonazepam, valproate, topiramate *Second-line:* lamotrigine, levetiracetam *To be avoided:* carbamazepine, oxcarbazepine	No guidance given	No guidance given
LKS	No guidance given	*First-line:* lamotrigine, valproate, steroids *Second-line:* levetiracetam, topiramate *Other drugs:* sulthiame *To be avoided:* carbamazepine, oxcarbazepine	No guidance given	No guidance given
CSWS	No guidance given	*First-line:* clobazam, clonazepam, ethosuximide, lamotrigine, valproate, steroids *Second-line:* levetiracetam, topiramate *To be avoided:* carbamazepine, oxcarbazepine, vigabatrin	No guidance given	No guidance given

The treatment recommendations shown have all been published since 2004.
BECTS, benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy); CAE, childhood absence epilepsy; CSWS, continuous spikes and waves during slow sleep; IGE, idiopathic generalized epilepsy; IOLE, idiopathic occipital lobe epilepsy (late-onset childhood occipital epilepsy – Gastaut type); JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; PS, Panayiotopoulos' syndrome (early-onset benign childhood occipital epilepsy – Panayiotopoulos type).
[a]The guidelines refer to treatment of TAS rather than CAE.

levetiracetam in a double-blind, placebo-controlled trial of 229 patients had at least a 50% reduction in GTCS compared with 45% treated with placebo [29].

Findings from other studies

There are numerous open studies, case series and case reports of the treatment of children with IGE, many of which are very small. Recent detailed reviews have been published by Hitiris and Brodie [30] and Bergery [31]. What follows is a summary of important clinical points from these reports.

Ethosuximide was the first of the 'modern' AEDs reported to be efficacious in 'petit mal'. A number of open, add-on, non-comparative studies were reported [30]. Overall these showed a seizure-free rate of just over 50% but the poor study designs make it difficult to determine what proportion of patients with absence epilepsy responded to the drug. Nevertheless,

ethosuximide is established as a first-line AED for TAS and therefore is similarly associated with CAE. It is not generally considered effective for GTCS and, therefore, neither is it considered effective for JAE and JME. However, Schmitt *et al.* [32], in a retrospective review of 238 patients with absences and 3-Hz spike–wave discharges, found that GTCS were no more likely to develop in those patients treated with ethosuximide than in those treated with other AEDs.

Sodium valproate has been assessed both in open non-comparative studies and in single-blind, placebo-controlled trials in both children and adults with TAS (with or without other seizure types) [31]. These suggest that valproate is efficacious for TAS with seizure-free rates of between 88% and 95%. Case series have also demonstrated good responses to sodium valproate in JME, with seizure freedom rates of 54–93%. The recently reported SANAD B trial compared treatment with sodium valproate, lamotrigine and topiramate (prescribed randomly but unblinded) in 716 children and adults in whom the treating physician considered sodium valproate to be the drug of first choice. Over 60% of patients with TAS had IGE. Sodium valproate was superior to both lamotrigine and topiramate in terms of time to treatment failure and to lamotrigine but not topiramate in terms of time to 12 months' remission. The authors concluded that sodium valproate was more efficacious than lamotrigine and better tolerated than topiramate [33].

Old reports of the use of acetazolamide suggested efficacy both as monotherapy and as add-on therapy for absence seizures and for GTCS in JME [34–36]. It has never been considered a first-line therapy but continues to be used occasionally as an adjunctive treatment in patients with drug-resistant IGE. Similarly, benzodiazepines, particularly clonazepam and clobazam, have been reported as effective in the treatment of both absences and JME [37,38]. Particular efficacy for clonazepam against MS is claimed [39].

Open studies suggest that lamotrigine is an effective treatment for childhood absence epilepsy [40–42], including for initial treatment. However, the slow titration recommended means that control is likely to be achieved more quickly with sodium valproate. Open studies also suggest efficacy of lamotrigine in JME. Morris *et al.* [43] reported its use in 63 patients who had failed on treatment with sodium valproate and found good response rates for GTCS, TAS and MS. However, some patients had an increase in MS, a problem which has also been reported by others [44,45].

Cross *et al.* [46] reported a small open study of topiramate for childhood absences. One child became seizure free, two improved at low dose and two showed no improvement. An open study has suggested efficacy of topiramate in JME [47].

A number of open studies of levetiracetam add to the evidence from controlled studies of its efficacy in IGE. Cavitt *et al.* [48] found it to be effective against typical absences and Verrotti as efficacious as initial monotherapy in JME [49].

Reports of the use of zonisamide in IGE in children are scant. However, a retrospective notes review of using it to treat teenagers and young adults with JME found evidence of efficacy [50].

For many years carbamazepine and phenytoin were considered less effective or ineffective in IGE and, more recently, evidence from case series has demonstrated aggravation of seizures in IGE by these drugs and other newer 'narrow spectrum' AEDs, including vigabatrin, gabapentin, oxcarbazepine, tiagabine and pregabalin. All of these drugs should generally be avoided in children with IGE [51,52]. However, it is possible that refractory GTCS may respond. Phenobarbital is sometimes useful against GTCS in the IGE but may exacerbate TAS. In such cases in which cost considerations are paramount, it may be an appropriate choice.

Recommendations from expert committees

According to the criteria of the ILAE treatment guidelines, the highest level of evidence available is level C for treatment of children with TAS and D for treatment of JME (Table 14.4) [3]. The AAN appraisal of the new AED found evidence of the effectiveness of lamotrigine for the treatment of newly diagnosed TAS and limited evidence of the effectiveness of lamotrigine and topiramate as adjunctive therapy for refractory seizures in IGE [4]. The recommendations of NICE and the US and European expert committees are summarized in Table 14.4.

Concluding remarks

Treating children and teenagers with IGE is usually very rewarding as the success rate is high and many, notably those with CAE, can often successfully discontinue medication. Given that these syndromes are quite common, the lack of robust evidence to guide therapy is surprising. In managing children with IGE, avoiding drugs with the potential to exacerbate seizures is extremely important. Failure to appreciate this leads to apparent refractory epilepsy. Although AEDs such as carbamazepine may successfully control GTCS in patients with IGE (this is not well researched), such drugs should certainly initially be avoided in treating IGE and then be used only with extreme caution.

There is a reasonable evidence base that sodium valproate, lamotrigine, topiramate, levetiracetam and to a lesser extent zonisamide are active against seizures in all IGEs. However, lamotrigine is not a good anti-myoclonic agent and will exacerbate myoclonic seizures in a minority of subjects. Ethosuximide is usually reserved for childhood absence epilepsy, given its narrow spectrum of activity. The choice of AED in any individual is likely to be determined by an evaluation of possible adverse effects and the physician's familiarity with the individual drugs. The most common dilemma is what drug to choose in females of childbearing potential. Fears over the teratogenicity of sodium valproate cause many physicians to choose alternatives, although it must be stressed that lamotrigine (which is often chosen) is not without teratogenic risks and the other newer agents have not been sufficiently evaluated. Overall, sodium valproate remains the most widely prescribed AED for the IGE. Levetiracetam is also efficacious, especially in JME. Levetiracetam, like sodium valproate, is active against photosensitive seizures. The adverse effect profiles of both topiramate and zonisamide mean, in the author's opinion, that neither is likely to become a first-line agent for treating IGE.

Monotherapy is usually effective. In those patients who fail to achieve remission with first-line monotherapy, a trial of a second (and even a third) monotherapy agent is usually appropriate. Beyond that, combinations of AEDs may be needed. A therapeutic interaction between sodium valproate and lamotrigine has been reported [40]. In JME, the addition of a benzodiazepine (clonaz-

epam is probably the best) may be helpful in abolishing troublesome myoclonic seizures in patients in whom GTCS and absences have already been controlled. A similar approach may be helpful in eyelid myoclonus with absences. However, this syndrome often proves very resistant to drug treatment.

Non-drug treatments, such as the vagal nerve stimulator and the ketogenic diet, are rarely needed or contemplated for IGE. There are no published trial data on their effectiveness.

Remission, although not guaranteed, is expected in CAE. Therefore, it is nearly always appropriate to attempt AED withdrawal after two seizure-free years. Indeed, earlier withdrawal may sometimes be reasonable. If relapse occurs, treatment can be restarted and a further attempt at withdrawal made after a suitable interval. For those syndromes in which the prognosis for eventual seizure remission is less certain, notably JAE, it is still nevertheless usually appropriate to attempt withdrawal after suitable discussions with the patient and family. It is often less disruptive if relapse occurs before reaching adulthood. For JME, in which relapse is expected, AED withdrawal should be attempted only if it is clear that the patient understands the risk of recurrence.

Treatment of idiopathic focal epilepsy syndromes of childhood

The ILAE currently recognizes benign childhood epilepsy with centrotemporal spikes (BECTS); early-onset benign childhood occipital epilepsy (Panayiotopoulos type); late-onset childhood occipital epilepsy (Gastaut type); and idiopathic photosensitive occipital lobe epilepsy (IPOLE). BECTS is more commonly called benign rolandic epilepsy. Early-onset benign childhood occipital epilepsy (Panayiotopoulos type) is manifested with autonomic symptoms (and is probably not an occipital epilepsy). It is increasingly referred to as Panayiotopoulos' syndrome (PS). Late-onset childhood occipital epilepsy (Gastaut type) can more conveniently be called idiopathic occipital lobe epilepsy (IOLE). Patients with IPOLE are photosensitive but, otherwise, its clinical features are similar to those of IOLE, thus IPOLE can be considered a subgroup of IOLE. The features of these syndromes are shown in Table 14.2. Although there are a number of other proposed idiopathic focal epilepsies occurring in childhood, these are not well characterized and will not be considered further here.

Findings from double-blind randomized controlled studies

Given how common BECTS and PS are, the lack of high-quality evidence regarding their treatment is surprising. There are no double-blind placebo-controlled studies of PS or IOLE.

There are two double-blind randomized controlled studies in BECTS. Both used a forced exit strategy. Rating *et al.* [53] studied 66 children with BECTS randomized to receive sulthiame (5 mg/kg/day) or placebo for 6 months. The primary outcome measure was the rate of treatment failure events (TFEs). TFEs were seizures 7 days or more into treatment, intolerable adverse events, development of another epilepsy syndrome or termination by parent or patient. Twenty-five out of 31 patients treated with sulthiame had no TFEs compared with 10 out of 35 treated with placebo ($P = 0.0002$). TFEs were mainly seizures (four in the sulthiame group and 21 in the placebo group). Approximately 40% of patients who remained on sulthiame had normal EEGs at the end of the study period. On further analysis, it was concluded that sulthiame led to normalization of the EEG in the majority of subjects treated and that this persisted in over one-half of patients [54]. Effects on quality of life and on cognition and language were not studied. Bourgeois *et al.* [55] reported (in abstract form) a double-blind study of 225 children with BECTS randomized to receive either gabapentin (30 mg/kg/day) or placebo. Treatment was for 36 weeks or until a TFE event occurred. This was defined as a secondary generalized tonic–clonic seizure, three partial seizures, status epilepticus or worsening of seizure activity. Time to TFE was longer for those given gabapentin but this was not statistically significant using the log-rank test but was significant using Wilcoxon's test. The Kaplan–Meier estimate of those completing the 36-week treatment phase was 57% and 44% for gabapentin and placebo respectively. Withdrawals for adverse effects were 3.5% for gabapentin compared with 0% with placebo.

Findings from other studies

Peters *et al.* [56] reported an important population-based study comparing the effects of treatment (44 children) with non-treatment (36 children) in BECTS. Patients were not randomized but physician advice was a major determinant of treatment choice. Treatment was with carbamazepine in 82% of patients. After treatment, 44% of patients became seizure free compared with 11% of untreated patients. There was evidence that treatment prevented secondarily generalized seizures but not focal seizures. All patients eventually became seizure free 4–14 years after diagnosis and there was no evidence of improvement in educational achievement, school satisfaction or social adjustment in the treated group. The authors concluded that a non-AED treatment strategy could be offered.

In recent years, a number of non-randomized, uncontrolled studies have reported the use of the newer AEDs in BECTS. These have suggested that topiramate, levetiracetam and oxcarbazepine may be efficacious [57–60]. However, the small numbers treated and/or the lack of controls limits their usefulness when deciding on AED treatment for a syndrome characterized by a low seizure count and spontaneous remission. Kang *et al.* [57] compared 45 patients with BECTS randomized to open treatment with topiramate monotherapy (mean dose 3.5 mg/kg/day) with 43 randomized to open treatment with carbamazepine monotherapy (mean dose 21.6 mg/kg/day). After 28 weeks' treatment, approximately 70% of patients were seizure free on both treatments but there was evidence of adverse cognitive function and behavioural problems in those treated with topiramate. Kossof *et al.* [61] reported a pilot study of six children with BECTS with impaired auditory comprehension and verbal memory. Significant improvements were seen following switching from existing AED treatment to levetiracetam. Tzitiridou *et al.* [60] reported evidence that treatment of BECTS with oxcarbazepine is effective not only in controlling seizures, but in normalizing the EEG and preserving cognitive and behavioural abilities.

Reports suggest that some children with BECTS treated with carbamazepine or lamotrigine develop learning problems or aggravation of seizures and/or induction of new seizure types [52]. However, a causal link is not firmly established. In the

author's opinion it is likely that some reported cases are coincidental.

There have been over 1000 children with PS reported in a number of large case series. These have included details of how children with the syndrome were managed. A variety of drugs has been used but there has been no detailed analysis of the effectiveness of individual agents. In the most recent report, 172 patients received AED treatment and 20 received no AED treatment [62]. Treatment was mainly with carbamazepine (112 patients), with smaller numbers receiving sodium valproate, phenobarbital, oxcarbazepine and clobazam. One hundred and fifty-two of those treated became seizure free after treatment, although 71 had had only a single seizure before treatment. In all patients seizures remitted within 1–6 years of onset.

Far fewer patients with IOLE have been reported. The largest series to date was of 33 patients with the syndrome, including five who were photosensitive on electroencephalography (four of whom had light-induced seizures) [63]. All were treated with antiepileptic drugs, with sodium valproate and carbamazepine being the most commonly used agents. About 80% of the patients were reported to be seizure free (on or off medication) within 2–7 years of seizure onset.

Atypical evolutions of PS and IOLE with the development of other seizure types and continuous spikes and waves during slow-wave sleep have been reported [64]. However, the relationship of this to AED treatment remains unclear.

Recommendations from expert committees

The recommendations of the ILAE and NICE, and the results of surveys of US and European physicians for the treatment of BECTS, PS and IOLE are summarized in Table 14.4. The lack of consensus is striking.

Concluding remarks

Both BECTS and Panayiotopoulos' syndrome are exceptionally benign syndromes, and there is no evidence that AED treatment alters their long-term prognosis. Many clinicians advocate managing most children with these syndromes without regular AED medication, drug treatment being reserved for those children whose seizures are particularly unpleasant because of their symptomatology or frequency or both [65]. Parental attitudes often play a significant role in determining which children receive regular treatment. An alternative to regular AED treatment is the provision of rescue medication such as rectal diazepam and oral midazolam to terminate prolonged seizures. There are no studies comparing the risk–benefit ratio of such a strategy.

Two justifications are sometimes advanced in favour of treating children with BECTS and/or PS with regular AEDs. First, some children with BECTS develop linguistic, cognitive and behavioural problems. In part, this may be a consequence of transient cognitive impairment during interictal discharges. However, to date there is no convincing evidence that AED treatment can prevent this: indeed, it may cause it [66]. Second, PS is reported occasionally to result in cardiorespiratory arrest [67]. However, it is reassuring that the risk of SUDEP is not increased in children with idiopathic epilepsies.

If regular AED treatment is used, the excellent prognosis of BECTS and Panayiotopoulos' syndrome means that AED drug withdrawal after a suitable seizure-free interval (usually 2 years) is appropriate. Some children will relapse and a further course of treatment may be appropriate. However, given the natural history of these epilepsies, it should be possible to achieve AED withdrawal prior to the age of 16 years. The EEG is not helpful in planning when to withdraw AEDs as persistence of EEG abnormalities long after clinical seizure remission is common.

Treatment considerations in IOLE are different, both because seizures are usually frequent and because remission is less certain. Regular AED treatment is nearly always indicated and, although it is appropriate to try to withdraw AED medication after a suitable seizure-free interval, withdrawal may not be possible in childhood. In a minority of those with the photosensitive form of the syndrome, in whom all seizures are precipitated by photic factors, avoidance of such factors may be sufficient. For the rest, regular AED treatment is indicated. For those on medication, persistence of photosensitivity is a useful indicator of the likelihood of relapse if medication is discontinued.

Treatment of epileptic encephalopathies

An epileptic encephalopathy is defined by the ILAE as: 'A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function'. These are epileptic disorders in which, in contrast to non-encephalopathic epilepsies, on-going seizure activity is considered to be the cause of progressive neurological decline with cognitive impairment, behavioural disturbances and, in some cases, the appearance of ataxia and pyramidal signs. The mechanism(s) underlying the neurological decline is unknown. The epileptic encephalopathies must be distinguished from neurodegenerative disorders. In the epileptic encephalopathies the occurrence and severity of the associated neurological deficits vary greatly between individuals and, to a considerable degree, unpredictably. The deficits can fluctuate according to seizure control and, if seizure remission is eventually achieved, further decline is not expected. It follows that effective treatment may be expected to improve the ultimate prognosis. However, proof that this is so is lacking.

The core epileptic encephalopathies encountered beyond infancy are the Lennox–Gastaut syndrome (LGS), the Landau–Kleffner syndrome (LKS) and the related epilepsy with continuous spikes and waves during slow-wave sleep (CSWS). Epilepsy with myoastatic seizures (Doose syndrome) and epilepsy with myoclonic absences (EMAs) behave as epileptic encephalopathies in some but not all affected children.

Myoclonic encephalopathy in non-progressive disorders is increasingly recognized as being a distinct epileptic encephalopathy but has its peak age of onset in infancy and will not be considered here. Important features of the epileptic encephalopathies are given in Table 14.3.

With the possible exception of LKS, it is rare for an epileptic encephalopathy to be diagnosed when the child first presents. Much more usually, the diagnosis becomes apparent after a period during which the clinician considered he was dealing with a more straightforward epilepsy. Consequently most children will already be on AED treatment. It is important to review this as drugs such as carbamazepine, which can exacerbate seizures in IGE, anecdotally may also do so in the epileptic encephalopathies.

Managing a child with epilepsy should never be just about AED treatment. However, this is particularly the case in the epileptic encephalopathies. Drug treatment will only be one aspect, and often not the most important aspect. Management should be undertaken by a multidisciplinary team which may need to include psychology, psychiatry, education, speech and language therapy, physiotherapy and occupational therapy. Joint neuropsychological and speech and language therapy assessment is particularly important in the diagnosis of LKS and its subsequent management. All children with epileptic encephalopathies will have special educational needs. Many will be appropriately educated in the mainstream sector but, for some, placement in a special school may be more appropriate.

Because of the intractable nature of seizures in the epileptic encephalopathies, most children are eventually treated with combination AED therapy. Although improved seizure control may be achieved using two or even three AEDs rather than monotherapy, there is no place for using more than three regular AEDs in any of the epileptic encephalopathies. In some children with LGS, seizures are exacerbated by drug-induced somnolence.

Non-AED treatments, including the ketogenic diet and vagal nerve stimulation, are used in the epileptic encephalopathies more than in other epilepsies. Steroid and immunoglobulins may also have a role in management. Resective surgery is very rarely an option but functional neurosurgery, principally callosotomy and multiple subpial transection, can be useful.

The EEG often plays a significant role in monitoring the effectiveness of treatment in the epileptic encephalopathies. Sleep recordings are essential for the detection of continuous spikes and waves in slow sleep, whether part of LGS or CSWS, and for determining whether a particular therapy has abolished it. It is often useful to determine how 'active' the EEG is in order to help decide whether further treatment is appropriate and to confirm the clinical suspicion of non-convulsive status epilepticus.

Seizure remission occurs in a few patients with epileptic encephalopathies but is expected to occur in LKS. Usually, AED therapy will be continued for some years in those seizure free, but eventual discontinuation of AEDs should be considered. Although not systematically studied, it is probable that the EEG is also helpful in this regard.

Lennox–Gastaut syndrome

Of all paediatric epilepsy syndromes LGS is probably the one whose definition is the most disputed and yet it is also the one that has attracted the most interest from pharmaceutical companies. In North America a broader definition is often used than in Europe. In particular, patients with prominent myoclonic seizures are included and nocturnal fast rhythms on EEG are rarely insisted upon. This is important when assessing the relevance of published drug trials.

Findings from double-blind randomized controlled studies

There have been five double-blind placebo-controlled trials in LGS. All involved the addition of the study drug to existing AEDs [68–72]. The populations studied included children and adults, used broad definitions of the syndrome and had maintenance phases of, at most, only a few months. Cinromide was not shown to be superior to placebo [68]. The other drugs – felbamate, lamotrigine, topiramate and rufinamide – all showed superior efficacy to placebo as summarized in Table 14.5. Open-label extension phases to the double-blind placebo-controlled trials of felbamate, topiramate and rufinamide all suggested that the effi-

Table 14.5 Summary of the results of double-blind, placebo-controlled randomized trials of the treatment of Lennox–Gastaut syndrome.

Drug	Population	Intervention	Key outcomes
Felbamate	73 subjects aged 4–36 years having at least 180 atonic or atypical absences in 8 weeks prior to baseline	*Felbamate versus placebo* (maximum of 45 mg/kg/day or 3600 mg/day, whichever lower) for 70 days	Mean change in total seizure frequency: 19% decrease versus 4% increase[a] Responder rate for total seizures: 50% versus 11%[a] Mean change in atonic seizure frequency: 34% decrease versus 9% decrease[a] Responder rate for atonic seizures: 57% versus 9%[a] Discontinuations due to adverse events: 1 versus 1
Lamotrigine	169 subjects aged 3–25 years with at least one seizure every 2 days	*Lamotrigine versus placebo* (dose dependent on concomitant valproate therapy and body weight) for 16 weeks	Median change in major seizure frequency: 32% decrease versus 9% decrease[a] Responder rate for major seizures: 33% versus 16%[a] Median change in drop attack frequency: 34% decrease versus 9% decrease[*] Responder rate for drop attacks: 37% versus 22%[a] Discontinuations due to adverse events: 3 versus 7
Topiramate	98 subjects aged 1–30 years with at least 60 seizures in month prior to baseline	*Topiramate versus placebo* (target dose approx 6 mg/kg/day) for 11 weeks	Median change in major seizure frequency: 26% decrease versus 5% decrease[a] Responder rate for major seizures: 33% versus 8%[a] Median change in drop attack frequency: 15% decrease versus 5% decrease[a] Responder rate for drop attacks: 28% versus 14% Discontinuations due to adverse events: none
Rufinamide	138 subjects aged 4–37 years with at least 90 seizures (including drop attacks and atypical absences) in month prior to baseline	*Rufinamide versus placebo* (target dose 45 mg/kg/day) for 84 days	Median change in total seizure frequency: 33% decrease versus 12% decrease[a] Median change in tonic–atonic seizure frequency: 43% decrease versus 1% increase[a] Responder rate for tonic–atonic seizures: 43% versus 17%[a] Discontinuations due to adverse events: 6 versus 0

The drug doses shown in the intervention column are those of the active test agent.
[a] $P < 0.05$.

cacy shown in the blinded studies was maintained [73–75]. However, a Cochrane Review concluded that the optimal treatment of LGS remains uncertain with no one drug shown to be highly efficacious [76].

Findings from other studies

There are very few reports of open uncontrolled studies of older AEDs used specifically to treat LGS. Conflicting results have been reported with bromides [77,78]. It has been reported that 1,5-benzodiazepines (such as clonazepam) are efficacious, particularly for myoclonic seizures, although tonic status may be precipitated [79–81]. Clobazam (a 1,5-benzodiazepine) was evaluated as add-on therapy in 31 children, 14 of whom had LGS. Twenty-five experienced a >50% reduction in seizures [82].

There are more reports of open uncontrolled studies and case series of the use of the newer AEDs in LGS. The following summarizes the more pertinent of these, concentrating on AEDs for which there are no data from randomized, double-blind controlled trials and on studies that give additional useful information over and above that obtained from randomized, double-blind controlled trials.

Livingston *et al.* [83] reported a reduction in seizures in one-half of 26 subjects with LGS treated with vigabatrin. Feucht *et al.* [84], in an open dose-ranging study of vigabatrin in 20 subjects with LGS, found that, at 12 months, eight became seizure free and nine had at least a 50% reduction in seizures. In contrast, Luna *et al.* [85] reported a single-blind study of vigabatrin in which only two out of seven subjects with LGS had at least a 50% reduction in seizures and four had a greater than 50% increase in seizures.

In an open-label pilot study of levetiracetam, which included four patients with LGS, two had a long-term seizure reduction, one had an increase in seizures and one withdrew from treatment [86]. In a case series, four out of six patients with LGS treated with levetiracetam had a 100% reduction in myoclonic and tonic–clonic seizures [87].

A postmarketing survey of zonisamide from Japan reported that 28% of those with West syndrome or LGS improved after treatment [88].

Donaldson *et al.* [89] reported a chart review of 16 patients with LGS treated with lamotrigine and found that although tonic, atonic, tonic–clonic and atypical absence seizures appeared to respond, myoclonic seizures did not.

Given the frequent poor response in LGS to conventional AEDs, less conventional therapies are often used. Several small, uncontrolled studies have suggested efficacy of both ACTH and prednisolone. Twenty-three out of 45 children with LGS treated with ACTH became seizure free for more than 10 days, although 10 subsequently relapsed within 6 months [90]. Seven of 10 patients with LGS treated with prednisolone for 12 weeks achieved seizure freedom [91]. However, a Cochrane review [92] found no evidence to support the use of steroids in the treatment of childhood epilepsy, other than West syndrome. Initial encouraging reports suggested efficacy of intravenous immunoglobulin in LGS. However, a subsequent single-blind placebo study in LGS failed to confirm this, as did a double-blind placebo-controlled study of its use in a group of mixed epilepsies which included children with LGS [93,94].

Lennox–Gastaut syndrome is one of the most frequent indications for the ketogenic diet. Neal *et al.* [95] reported a trial of the diet in 145 children who had at least daily seizures. The most common syndrome diagnosis (n = 14) was LGS. Patients were randomized to receive the diet immediately or after 3 months. After 3 months, the mean percentage of baseline seizures was significantly lower in those on the diet. Thirty-eight per cent on the diet had a >50% reduction in seizures compared with 6% not on the diet. Numbers were too small to analyse by syndrome but there was no significant difference in efficacy between symptomatic generalized or symptomatic focal syndromes.

Resective surgery has an extremely limited role in the LGS. Subjects with focal or unihemispheric disease may develop LGS and case reports suggest that they may be exceptionally amenable to surgical treatment. Corpus callosotomy can be used for the treatment of atonic and tonic drop attacks, seizure types which characteristically occur in the LGS. A recent study from Taiwan reported that 68% of patients (children and adults) had at least a 50% reduction in seizures following anterior callosotomy and that this was not dependent on whether or not West syndrome had preceded LGS [96], although the duration of the follow-up period and the effect on different seizure types was not reported. Other studies have shown that, although the initial effect is often good, relapse is common. Callosotomy is, therefore, now only rarely used. In several small studies, which included patients with LGS, the vagal nerve stimulator is reported to have led to a >50% decrease in seizures in 37–73% of patients. A retrospective database analysis of 552 patients with LGS evaluated the response to the vagal nerve stimulator in patients with LGS naive to surgery versus those with a previous callosotomy. In those with no prior surgery, 50% had >50% reduction in seizure at 3 months and 55% at 18 months [97]. Results were similar in those with a prior callosotomy.

Recommendations from expert committees and concluding remarks

Recommendations for the treatment of LGS made by NICE, along with the results of surveys of US and European physicians, are shown in Table 14.4. LGS is best treated using broad-spectrum AEDs and sodium valproate is the usual initial choice. If, as is usually the case, seizure control remains poor, other AEDs such as lamotrigine, topiramate, felbamate and rufinamide have been shown to be efficacious in randomized controlled studies. However, given its potential for serious side-effects, felbamate is not an appropriate early choice. Similarly, lamotrigine should probably be avoided if myoclonic seizures are prominent. Although regular benzodiazepines may be helpful, their usefulness for treatment of episodes of non-convulsive status epilepticus means that they may be best kept in reserve. Carbamazepine, phenytoin, oxcarbazepine, pregabalin, tiagabine and gabapentin are best avoided in LGS as these drugs can exacerbate seizures.

There is, as yet, no consensus as to when less conventional therapies should be tried. The ketogenic diet and vagal nerve stimulator should probably be considered earlier than is often the case – possibly after two or three AEDs have been tried. Realistic goal setting, with quality of life, rather than seizure freedom, is paramount. There are some children with LGS in whom AED treatment appears to achieve nothing, and in a few cases, it is appropriate to wean them off all AEDs.

Doose syndrome

There are no randomized controlled studies of any treatment for Doose syndrome and the best evidence available is from case series. As it is classified as an IGE, the general principles outlined above for management of IGE apply. In particular, drugs which may exacerbate IGE should be avoided.

Sodium valproate is generally considered the first-line AED for Doose syndrome, although the evidence base for this is poor. Other older drugs that are reported to be efficacious include ACTH, ethosuximide and benzodiazepines. Of the newer antiepileptic drugs, lamotrigine, sometimes combined with sodium valproate, is often used. In a series of eight patients with the Doose syndrome, seven became seizure free on lamotrigine and there are no reports of lamotrigine exacerbating seizures in Doose syndrome [98]. In a retrospective review of six patients with Doose syndrome treated with add-on topiramate, all but one improved, with three having a greater than 80% reduction in seizures [99].

Particular efficacy of the ketogenic diet is claimed in Doose syndrome [100]. Caraballo [101] reported 30 patients with Doose syndrome, 11 of whom were treated with the ketogenic diet. At 18 months, six remained on the diet, two were seizure free, two had a 75–99% reduction in seizures and two experienced a 50–74% reduction in seizures. A chart review of 33 patients with Doose syndrome is reported which was carried out to assess which treatments were associated with the patient becoming seizure free for more than 6 months. Seizure freedom was achieved in 30% of those treated with the ketogenic diet, 25% of those treated with ethosuximide, 23% of those treated with topiramate, 18% of those treated with lamotrigine and 10% of those treated with sodium valproate. Treatment with no other drug (including levetiracetam, carbamazepine and benzodiazepines, among others) led to seizure freedom [102]. There is one report of myoclonic status epilepticus in Doose syndrome apparently provoked by levetiracetam [103].

The recommendations of NICE for the treatment of Doose syndrome are shown in Table 14.4.

Landau–Kleffner syndrome and the syndrome of continuous spikes and waves in slow sleep

The Landau–Kleffner syndrome (LKS) and the syndrome of continuous spikes and waves during slow sleep (CSWS) were described as separate syndromes but they share a number of common features. Continuous spikes and waves in slow sleep is a prerequisite for CSWS but, although common in LKS, is not a prerequisite for its diagnosis. Both are rare and there are no randomized controlled trials which help guide their management. In CSWS the epileptic seizures are often frequent and difficult to treat. In LKS, seizures are often infrequent and the language deficits and behavioural problems are usually of more concern than the seizures.

There are anecdotal reports that certain AEDs usually active in focal epilepsies, notably carbamazepine, may exacerbate LKS and CSWS. This and other drugs, such as oxcarbazepine, vigabatrin, tiagabine and gabapentin, are probably best avoided. It is sometimes said that 'conventional AEDs' have little, if any, role in these syndromes. However, most clinicians probably treat with at least one or two of them before trying other treatment modalities. Sodium valproate is probably initially used by most clinicians, although other conventional AEDs with broad spectrums of activity may also be worth trying. Anecdotally good results have been claimed for ethosuximide, benzodiazepines (administered rectally) and sulthiame [104,105].

Steroid medication, including oral prednisolone, intravenous methylprednisolone and ACTH are reported in relatively small case series to be beneficial in both LKS and CSWS [106–108]. It is usually advocated that they should be tried early on the clinical course. There is no consensus as to the most appropriate regimen. Relapses are common and some children require repeated courses, increasing the risk of adverse effects. The latter can be minimized by using the smallest dose possible (often alternate-day treatment). Success is also claimed for the use of intravenous immunoglobulins [109] and vagal nerve stimulation [110].

Eventual remission of seizures is usual in LKS. Therefore, although drug treatment is often required for many years, eventual withdrawal of such treatment can usually be achieved. For cases in which CSWS has been demonstrated, the EEG is likely to be useful during follow-up and in determining how long to continue drug treatment.

In LKS the epileptogenic focus is usually in one or other of the superior temporal gyri. Because this is an area of eloquent cortex, resective surgery is not an option. However, the technique of multiple subpial transections has been pioneered by Morrell for treatment of the syndrome and good results have been obtained in other centres as well [111,112]. However, even in those children who respond quickly, age-appropriate language appears to be only occasionally achieved. Reports suggest that earlier surgery is associated with a better functional impact. The management of the cognitive, language and behavioural co-morbidities in LKS and CSWS requires the input of other professionals, including speech and language therapists and child psychiatrists. The recommendations of NICE for treatment of LKS and CSWS can be seen in Table 14.4.

Myoclonic absence epilepsy

Treatment of this rare syndrome is guided by information from case series. Sodium valproate and ethosuximide, particularly in combination, are the AEDs most frequently mentioned. Achieving good seizure control is said to be associated with a better long-term cognitive outcome, although the evidence for this is not particularly robust. Lamotrigine, benzodiazepines and acetazolamide have also been recommended. The syndrome is listed by the ILAE as an IGE, and other AEDs such as topiramate and levetiracetam may also be appropriate, although narrow-spectrum agents, including carbamazepine, should be avoided. The effect of other therapies, such as steroids, immunoglobulins and the vagal nerve stimulator, is not reported.

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15 Management of Epilepsies Associated with Specific Diseases in Children

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Despite the great advances in medical knowledge there remains a tension between a purely empirical approach to treatment in epilepsy and treatment guided by a knowledge of the underlying aetiology. Much of therapeutic medicine remains empirical, but there is nonetheless general, if not universal, agreement that an understanding of the aetiology informs therapeutic decisions in a useful way. The multiple axes diagnostic scheme proposed by the ILAE in 2001 [1] encourages this approach. This chapter will consider the management of epilepsies in which there is a specific known aetiology. For most of the conditions considered, the level of evidence on which to base treatment is low and based on expert opinion and case reports.

The biggest impact on treatment in recent years has been as a result of the great improvements in neuroimaging. This has enabled the recognition of an increasing number of malformative, neoplastic or destructive causes of epilepsy that previously were difficult to diagnose in life. This in turn has improved the understanding of the natural history of many symptomatic epilepsies and the identification of good candidates for epilepsy surgery. Medical advances have been slow; however, alongside (and sometimes aided by) the improvements in imaging have been the rapid developments in molecular genetics. The gene mutations responsible for a growing number of conditions that cause, or are associated with, epilepsy have been identified. The next stage is to understand the functional effects of these mutations and devise interventions that may modify or reverse them.

For all of the conditions considered below, the basic principles of good epilepsy management should be followed. In particular the following questions should be considered:

1 Are the events that treatment is being considered for epileptic?
2 Is treatment necessary?
3 Could this treatment aggravate the seizures?

An awareness that non-epileptic paroxysmal disorders occur in many of these disorders is important. For some of the disorders considered below surgery may have a role. As most of these disorders are rare, early referral to a paediatric epilepsy surgery centre is important. If surgery is going to be of benefit, in general the earlier in the natural history of the epilepsy, the better will be the neurodevelopmental outcome.

Important co-morbid conditions in which epilepsy is common will be considered before discussing specific aetiologies.

Epilepsy in cerebral palsy

Epilepsy is common in cerebral palsy (CP), with reported prevalence rates ranging from 10% to 80%. The frequency is different depending on the type of CP: 50–80% for spastic quadriplegia, 50% for hemiplegia and 10–20% for diplegia [2,3].

Children with both epilepsy and cerebral palsy are much more likely to be mentally retarded than those with cerebral palsy without epilepsy. Any seizure type can occur, and common idiopathic epilepsies may also be present by coincidence. In the severely brain-damaged child with quadriplegic CP, many types of non-epileptic events may co-exist, such as myoclonus, startle, dystonia and gastro-oesophageal reflux or other pain-related behaviours. The EEG in some children with severe brain injury may always show multifocal paroxysmal abnormalities and thus diagnosis of which events are seizures may be very difficult. Avoidance of overtreatment is important.

No one antiepileptic drug (AED) has been shown to be superior to another in CP. However, drugs that may aggravate myoclonic seizures in IGEs may also have this effect in children with CP. Refractory epilepsy in hemiplegic CP may benefit from surgery [4,5].

Epilepsy in intellectual disability

The prevalence of epilepsy in children with severe intellectual disability is high (23–45%) [6]. Such children often have multiple co-morbidities that may impact on the diagnosis and management of epileptic seizures. Specific factors relating to the intellectual disability need to be considered:

- Behavioural problems are common but sometimes have an epileptic basis.
- Communication difficulties limit reporting of experiential aspects of seizures and adverse effects of AEDs.
- Adverse behavioural or cognitive effects of AEDs are probably more common.

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- Non-epileptic paroxysmal events are common and often coexist with epilepsy.
- Sleep disturbance is common and may in turn aggravate epileptic seizures.
- Sedative AEDs should be avoided as they may aggravate both cognitive problems and seizures [7].
- There may be a higher risk of accidents and injuries, and avoidable risk factors should be identified and minimized.

Most of the published studies of AED use in children include a high proportion of children with intellectual disabilities and severe epilepsy syndromes, thus the findings of these studies are generally applicable to this population. However, there are few specific research data on AED use in those with intellectual disabilities.

In general, broad-spectrum AEDs should be used and monotherapy should be the aim where possible. The presence of intellectual disability should not preclude consideration of surgical treatment.

Epilepsy in autism

The prevalence of epilepsy in autism is around 30–40% [8–10].

There is a complex inter-relationship between epilepsy and autism. In disorders such as Landau–Kleffner syndrome the autistic features are one of the primary manifestations of the epileptic disorder. In tuberous sclerosis the severity of the epilepsy correlates closely with the autism but is not the sole determinant.

Paroxysmal EEG abnormalities are seen in up to 60% of patients, many of whom do not have clinically apparent epileptic seizures [11,12]. Some children with autism appear particularly susceptible to adverse effects of AEDs. On the other hand, there have been many, largely anecdotal, reports of improvement in the affect on children with autism when they are started on AEDs [13]. Double-blind placebo-controlled trials of lamotrigine or levetiracetam, however, demonstrated no benefit [14,15].

If the epileptic seizures are not overt and there is uncertainty as to the contribution a paroxysmal EEG is making to autistic features, the decision to start an AED needs careful consideration. Assessing the outcome of treatment may require serial behavioural or neuropsychological evaluations, speech and language assessment and/or prolonged EEG recordings.

Epilepsies due to specific aetiologies

Chromosomal disorders

An increasing number of chromosomal disorders have been identified in children with epilepsies [16,17]. The epilepsy phenotypes are in some cases highly characteristic. The chromosomal abnormalities often cause dysmorphic features, brain malformations and other clinical features that may be independent of the epilepsy. It is beyond the scope of this chapter to consider all the chromosome disorders associated with epilepsy. In some disorders epilepsy is almost invariable, whereas in others it is only an occasional occurrence. In some, such as ring chromosome 20, the epilepsy is usually drug resistant.

Down syndrome

Epilepsy in Down syndrome may be secondary to an acquired brain insult (for example perinatal hypoxic ischaemic encephalopathy related to congenital heart disease or CNS infection) or due to the chromosomal abnormality itself. In general, the prognosis for seizure control is good where the seizures are of unknown cause, and for epileptic spasms, which are probably the most common seizure type in Down syndrome [18–20]. Spasms may respond to steroid or conventional AED treatment. There is some evidence that early treatment of spasms results in an improved neurodevelopmental outcome [21]. Late-onset epilepsies, however, may be drug resistant.

Angelman's syndrome

Epilepsy occurs in up to 90% children with Angelman's syndrome [22,23]. The onset is usually in infancy and it is often drug resistant. The common seizure types are atypical absences, myoclonic and generalized tonic–clonic. Status epilepticus (variously called non-convulsive or myoclonic) occurs in up to 50% [23,24]. Non-epileptic myoclonus is also common.

The combination of valproate and clobazam has been reported as particularly effective in case review series [22,25]. Long-term follow-up data, however, are not available. Benzodiazepines may be effective for episodes of status but not always. There are case reports of good responses to levetiracetam, lamotrigine and the ketogenic diet. Vigabatrin or carbamazepine may aggravate myoclonus [23,26].

Rett's syndrome

Epilepsy is common in Rett's syndrome, with a reported prevalence of 70%. Seizures may be drug resistant. However, it is important to recognize that non-epileptic attacks, such as hyperventilation, Valsalva manoeuvres, syncopes and stereotypes, are common and may be misdiagnosed as epileptic phenomena. Epileptic seizures may also be precipitated by hyperventilation in some children. Avoidance of overtreatment is therefore important.

CDKL5 mutation and epilepsy

The epilepsy phenotype associated with *CDKL5* mutations has recently been described in some detail. In the early stages most patients achieved seizure control on one or two first-line AEDs. Thereafter, an epileptic encephalopathy with epileptic spasms that was resistant to corticosteroids developed in just under one-half of patients. Interestingly, on long-term follow-up 7 out of 12 patients reported that they no longer had epilepsy [27].

Malformations of cortical development

Advances in neuroimaging have led to the identification of cortical malformations as the cause of epilepsy in many patients and to the recognition of malformation syndromes, which in many cases have a genetic basis.

The more severe malformations tend to be associated with refractory epilepsies in which, with a few exceptions, there are few data to recommend one treatment over another. On the other hand, in refractory focal epilepsies, identification of a focal malformation may lead to successful surgical treatment.

Shortly after its introduction vigabatrin was recognized as having particular efficacy in epilepsies caused by cortical malformations and particularly in tuberous sclerosis (TS) (see below). The concerns about visual field defects have greatly restricted its use outside patients with TS. In the author's view, the adverse consequences of refractory epilepsy greatly outweigh the potential adverse effects of a visual field constriction and vigabatrin should be more frequently used.

In TS, on the other hand, there is considerable evidence of the value of vigabatrin, particularly in the treatment of epileptic spasms. This includes data from several randomized controlled trials (RCTs). Cessation of epileptic spasms occurred in 90–100% of patients [28,29]. Most of these studies are short term, but long-term benefit has been described [30]. Other seizure types may also respond well to VGB. There are few data on the relevance of other AEDs in TS; however, topiramate, levetiracetam and zonisamide have been reported to be of benefit [31]. The ketogenic diet appears as effective in TS as in other resistant epilepsies [32]. With the exception of TS, no single AED has shown superiority in treating epileptic seizures caused by cortical malformations. Anecdotal reports suggest that ethosuximide has been of particular value in some epilepsies due to polymicrogyria.

Surgical resection of epileptogenic tubers has a growing place in the management of epilepsy due to TS. The best outcomes are following resection of a single tuber from which the majority of seizures have been shown to arise, with up to 90% seizure freedom reported and significant improvements in quality of life [33–35]. However, multifocal resections guided by invasive and/or intraoperative EEG monitoring may have benefit [36]. Longer-term follow-up data will be necessary before the role of surgery is fully established.

The particular efficacy of vigabatrin in TS and the possibility of antenatal detection, or detection in early life before seizures have started, has led to a discussion about 'prophylactic' treatment with vigabatrin (or other AEDs) and the proposal for a trial to study this [37,38].

Hypothalamic hamartoma and intractable epilepsy

Hypothalamic hamartoma (HH) with intractable (often gelastic) seizures is a rare but important syndrome that nearly always presents in childhood and may present with neonatal-onset seizures. The classical seizure type is gelastic (or dacrystic), but seizures often progress into a severe epileptic encephalopathy with frequent mixed seizure types, often with focal features. Antiepileptic drugs are generally ineffective. The importance of diagnosing this syndrome is that surgical treatment is effective in many patients. Different surgical approaches have been advocated including endoscopic resection, thermocoagulation and Gamma Knife® surgery. Follow-up studies have shown up to 66% achieving seizure freedom or only rare seizures with open craniotomy or endoscopic approaches [39,40] (see Chapter 75).

Vascular malformations

Sturge–Weber syndrome

Epilepsy occurs in 80% of children with Sturge–Weber syndrome (SWS) and is intractable in 60–75%. Seizures may respond well to AEDs [41]. There is a significant risk of status epilepticus and prolonged seizures should be treated aggressively because of the risk of postictal hemiplegia. When seizures are refractory, hemispherectomy (or multilobar resections) to remove all of the pial angiomatosis offers the only prospect of seizure control (see Chapter 73). The decision to proceed to surgery depends on several factors, such as the neurodevelopmental stagnation, a progressive hemiplegia and evidence of progressive shrinkage of the affected hemisphere. The seizure outcome from resective surgery is excellent [42].

Other vascular malformations

Arteriovenous malformations (AVMs) present with epileptic seizures as the first clinical feature in around 20% of cases. In general, because of the cumulative life-long risk of bleeding, once an AVM has been identified treatment is recommended. This may take the form of resective surgery, embolization or Gamma Knife surgery. The place of surgery depends on the site and size of the malformation and its vascular anatomy. Surgical resection of AVMs carries significant risks. Surgical resection of cortical AVMs abolishes seizures in up to 50% of patients [43]. No single AED has shown superiority over another in the long-term management.

Cavernomas

Cavernous angiomas or cavernomas are a rare cause of epilepsy but present with epileptic seizures in up to 80% of cases. Multiple cavernomas may be present and are commonly familial, and new lesions may develop with time. Seizures are often difficult to treat and, if refractory, surgical resection results in seizure freedom in up to 85% patients. Gamma Knife surgery may also be effective for lesions in functionally important areas. The surgical resection of individual cavernomas in patients with multiple lesions can be carried out, but the presence of other lesions limits the prophylactic value of surgery.

Mesial temporal lobe epilepsy

Mesial temporal lobe epilepsy (MTLE) is recognized as a syndrome in the ILAE 2001 diagnostic scheme. Many patients with MTLE have hippocampal sclerosis on MRI and this can be regarded as the probable cause of the epilepsy. However, in familial MTLE, hippocampal sclerosis is not present in all affected individuals, suggesting that other factors (genetic or environmental) contribute to the epilepsy [44]. The combination of MTLE and hippocampal sclerosis is a well-characterized syndrome. A recent prospective study of children with TLE demonstrated that long-term remission on medical treatment for children with TLE does not occur in the presence of an imaging abnormality and that early surgery has a high success rate [45].

Epilepsy due to brain tumours

Brain tumours are a rare cause of epilepsy in children. Epileptic seizures, however, are common in children with supratentorial tumours and are often the presenting feature. Low-grade cortical tumours, such as ganglioglioma and dysembryoplastic neuroepithelial tumours (DNETs), are important causes of intractable focal epilepsies that may be surgically treatable. There are two aspects

of management that need to be considered when a possible tumour is demonstrated on a scan in a child with a focal epilepsy: tumour management and epilepsy management.

Tumour management

The choice of therapy depends on various individual factors. In general, though, if the signs and symptoms are rapidly evolving, or there is evidence of radiological progression on sequential scans, then a tissue diagnosis and/or primary resection becomes the priority. Surgical planning should consider the epilepsy management even if the primary reason for surgery is oncological. For example, it may be appropriate to plan total resection rather than a biopsy if the tumour is in a site where this can be achieved with low risk of new damage. Chemotherapy and/or radiotherapy alone is unlikely to cure the epilepsy.

Epilepsy management

If the epilepsy is the primary clinical feature and sequential scans are stable, then the decision to proceed to surgery can be guided by similar criteria as for other lesional focal epilepsies (see Chapter 77). The outcome from complete resection of a neoplastic lesion causing refractory epilepsy is excellent, with up to 80% of patients becoming seizure free [46–48]. Although incomplete resection may produce a significant benefit, the long-term outcome is less favourable and seizures will recur in many patients [49].

No one AED has proven superior in the management of epilepsy due to brain tumours. A recent report suggests that levetiracetam is well tolerated and effective in adults with brain tumours, although the majority of these were high-grade gliomas [50], and there is no convincing evidence that levetiracetam is any better or worse than other AEDs in this situation.

Epilepsy caused by CNS infection

Central nervous system infection is an important cause of epilepsies worldwide. Prevention of the initial infection through public health programmes and early management of infections have the potential to reduce the incidence of epilepsy significantly. In general, the development of an epilepsy correlates with the degree of CNS damage sustained during the acute illness. However, for some infections that do not have distinct acute and chronic phases this is less clear cut. In these situations, as well as AEDs, treatment of the cause of the infection may improve seizure control, for example in neurocysticercosis or tuberculoma. Refractory focal epilepsy following meningitis or encephalitis may benefit from epilepsy surgery. The best outcome can bee seen in those with MTLE with unilateral hippocampal sclerosis [51].

Rasmussen's encephalitis (chronic focal encephalitis)

Rasmussen's encephalitis (RE) is a rare cause of intractable epilepsy in children associated with a progressive hemiparesis, cognitive decline and hemispheric atrophy. AED therapy is usually ineffective, although temporary response may occur and some seizure types in an individual may respond well while others remain refractory. No AED has been proven to be better than another. Because of the severe and frequent seizures, including epilepsia partialis continua, there is a risk of overtreatment with resulting adverse effects. The natural history of RE is for it to burn itself out after many years (usually but not always), with severe cognitive and motor deficits but not necessarily seizure freedom. Because the aetiology is thought to be an inflammatory process with an immunological basis, various immune therapy approaches have been tried. These include steroids, immunoglobulins, plasmapheresis and other immune suppressive therapy. There is evidence that there may be an initial response to treatment with either intravenous steroids or immunoglobulins [52,53]. However, long-term response is disappointing.

The only treatment that has been shown to be of lasting benefit is hemispherectomy (or hemispheric disconnection) [5,54,55]. Limited resections or callosotomy are not of benefit. In theory, early surgery is the optimal treatment; however, time is often needed both to establish the diagnosis and to prepare the child and family for the procedure. In particular, it may be difficult for the family to agree to surgery before a hemiplegia or hemianopia is severe or permanent or if the seizures are temporarily improved with medical treatment. A further consideration is that if the dominant hemisphere is involved, shift of language to the non-dominant hemisphere is unlikely to occur following hemispheric surgery after the age of 10 years.

Hemiconvulsion, hemiplegia, epilepsy syndrome

The hemiconvulsion, hemiplegia, epilepsy syndrome (HHE) syndrome has become rarer in recent years, presumably because of better emergency treatment of prolonged convulsive seizures [56]. The epilepsy in this syndrome is often refractory to AEDs and no single AED has been shown to be superior to another. Surgery may be of benefit, particularly if mesial temporal lobe seizures predominate and there is hippocampal sclerosis [57]. Extratemporal resections including hemispherectomy may also be of some benefit. Determining the extent of resection planned may require invasive electroencephalographic monitoring [56].

Metabolic disorders

Epilepsy is a feature of a large number of neurometabolic disorders – sometimes an occasional feature and sometimes the most prominent feature [58]. In a small number of metabolic disorders, a specific treatment directed at the underlying biochemical defect will control the seizures and greatly improve the neurodevelopmental outcome, even if this is not always returned to normal. Identifying these disorders is therefore a priority in the investigation of children (particularly infants) with epilepsies (Table 15.1) [59–93].

In general, when a metabolic disorder has been diagnosed, the aim of treatment should be to treat the underlying metabolic problem where possible. If seizures are associated with hypoglycaemia, then this should be corrected and the cause treated, for example with dietary measures in fatty acid oxidation disorders. In disorders such as phenylketonuria, there is good evidence that this approach is effective both in preventing the development of seizures and in controlling them if they have occurred.

Table 15.1 Disorders presenting in infancy with epileptic seizures for which there is a specific non-AED treatment.

Disorder	Diagnostic test	Treatment
Glucose transporter deficiency type 1 (Glut–1) [59]	CSF/plasma glucose ratio less than 0.5 Mutation in *Glut1* gene	Ketogenic diet
Biotinidase deficiency	Biotinidase assay – blood	Biotin
Pyridoxine deficiency [60]	Trial of treatment Urinary–α-aminoadipic semialdehyde dehydrogenase (a-AASA) Mutation in antiquitin gene	Pyridoxine
Pyridoxal 5′-phosphate deficiency [61]	Trial of treatment CSF neurotransmitters	Pyridoxal phosphate
Serine biosynthesis disorders [62]	Low CSF serine levels Enzyme activity in fibroblasts	Serine
Fatty acid oxidation disorders	Urine organic acids Blood acyl carnitines	Diet
Creatine synthesis disorders [63]	MRS Urine guanidinoacetic acid	Creatine

AED, antiepileptic drug; CSF, cerebrospinal fluid; MRS, magnetic resonance spectroscopy.

Having excluded the disorders shown in Table 15.1, and assuming that the underlying metabolic disorder is being treated (when possible), then the general approach to the management of epilepsies caused by neurometabolic disorders is the same as for epilepsies of other aetiologies. If a diagnosis of Alpers' disease is possible then the use of valproate may precipitate fatal hepatic failure and is contraindicated. Although there are theoretical reasons for avoiding valproate in other mitochondrial diseases, there is no evidence that this is necessary. On the other hand, valproate is less well tolerated in fatty acid oxidation disorders. Phenobarbital should be avoided in GLUT1 deficiency as it may interfere with transport of glucose into the CNS.

The ketogenic diet is beneficial in pyruvate dehydrogenase deficiency but is contraindicated in pyruvate carboxylase deficiency.

Progressive myoclonus epilepsy syndromes

Progressive myoclonus epilepsies are neurodegenerative disorders in which myoclonus (epileptic and non-epileptic) is particularly prominent. Progressive neurological deterioration, particularly ataxia, is common and other epileptic seizures are prominent. In children the ceroid lipofuscinoses are probably the most common aetiological group. The management of these disorders is challenging and as the disease progresses becomes increasingly palliative. There are, however, some treatments that may be beneficial.

Drugs to avoid in progressive myoclonic epilepsies

It is now well documented that phenytoin severely exacerbates both the epileptic seizures and the cognitive function of patients with Unverrict–Lundborg disease (synonym: Baltic myoclonus) [64]. The reasons for this are not clear. Other AEDs that commonly aggravate myoclonic seizures, such as carbamazepine, oxcarbazepine, tiagabine and vigabatrin, are relatively contraindicated [65].

Antiepileptic drugs that may be of benefit in progressive myoclonus epilepsies

The common seizure types in progressive myoclonic epilepsies (PMEs) are myoclonic, focal and generalized tonic–clonic and reflex seizures, especially light induced. The most useful AEDs, therefore, are those with a broad spectrum and efficacy in photosensitivity. Valproate is probably the most useful AED and there is an increasing number of reports on the efficacy of levetiracetam [66,67].

Benzodiazepines may be of benefit but have the well-recognized problems of tolerance, cognitive adverse effects and difficulty in withdrawal, which can limit their value. The combination of valproate with clobazam or clonazepam may provide considerable benefit [68]. Recent reports have shown that topiramate or zonisamide may also be of benefit [69,70].

Several studies have demonstrated efficacy of piracetam for the myoclonus [71].

As with many of the disorders considered in this chapter, awareness of the risks of overtreatment is crucial. Escalating doses of AEDs may aggravate both epileptic and non-epileptic seizures. On the other hand, worsening irritability accompanied by myoclonus may be better treated with sedative agents, such as opiates or intermittent chloral, than inappropriate AEDs.

Epilepsies caused by specific gene mutations

In recent years, an increasing number of gene mutations, almost all coding for ion channel proteins, have been identified as causing or associated with various 'idiopathic' epilepsy syndromes. The most clinically relevant epilepsy gene identified so far is the *SCN1A* gene, coding for the α_1-subunit of the neuronal sodium channel. Mutations in this gene are present in up to 80% of children with Dravet's syndrome (see Chapter 13). Stiripentol has been shown in a randomized, placebo-controlled study to be effective in treating seizures in children with Dravet's syndrome [72]. In this study it was not known which children had the *SCN1A* mutation, and it is not known how the response to stiripentol relates to the functional abnormalities caused by the mutation. However, this may be the first example of an AED choice that can be targeted to a specific genetic abnormality. There is also evidence that AEDs which block sodium channels, such as phenytoin, lamotrigine or carbamazepine, may aggravate seizures in Dravet's syndrome and should be avoided [73].

The functional effects of most identified mutations are not fully understood; however, it is to be hoped that a fuller

understanding of these effects will lead to the development of rational treatments directed at reversing or attenuating the functional abnormality.

Summary

In this chapter, the influence of the aetiology of an epilepsy on its management has been considered. Many of the disorders considered are individually rare, and robust RCTs of therapies will prove very difficult to perform. However, a small number of such studies have been achieved. The impact of epilepsy surgery illustrates that if a very effective treatment is available, an RCT is not always necessary.

Most of the evidence on AED treatment for the conditions considered above is therefore based on expert opinion and anecdotal reports. The management of an epilepsy is not simply a question of which AED to use: understanding the aetiology has wider implications than this. A knowledge of the natural history enables realistic therapeutic goals to be set and an appropriate prognosis to be given. Early recognition and management of associated medical complications and co-morbidities is possible and this may prevent longer-term problems (both medical and non-medical). In many of the disorders discussed above, non-epileptic paroxysmal events occur, some of which are quite specific to a given disorder. Recognition of this prevents inappropriate and excessive AED use and allows appropriate treatment strategies.

Appropriate genetic counselling can be given to families, and antenatal detection or early diagnosis is possible for an increasing number of diseases. Therapeutic research trials will be most meaningful if patients with the same aetiology can be compared. For many parents and families, understanding the cause of their child's epilepsy helps them to adjust and adapt to it, even if treatment remains difficult.

In most of the conditions considered here, the epilepsy is difficult to treat and often associated with structural brain abnormalities. Thus, in tuberous sclerosis, for instance, identification of the causative genes and a growing understanding of their functions is beginning to suggest therapeutic approaches. Unravelling the causes of idiopathic epilepsies remains an enormous challenge. However, as an increasing number of epilepsy genes are identified, it is not unrealistic to predict that specific treatments will be developed targeting the functional abnormality caused by the abnormal genes.

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16 Management of Epilepsy in the Elderly

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Introduction

Seizures and epilepsy are the third most common neurological disorder affecting older adults, after stroke and dementia. As many factors can complicate treatment decisions in elderly patients, management of seizures and epilepsy in this age group warrants special consideration. Age-related physiological changes, both systemic and neurological, require care in the selection of anticonvulsant medication, as well as in dosing regimens. Co-morbid conditions and co-medications, which are commonly present, increase the likelihood of drug interactions. Age-related changes in drug handling and central nervous system (CNS) pharmacodynamics can all reduce efficacy or increase the risk of intolerable side-effects in this age group. Although the primary goals of treatment, including freedom from seizures, absence of adverse effects and the maintenance of a high quality of life, are the same for all patients with epilepsy, the aforementioned issues are significant considerations when making management decisions in the elderly population. Dealing with these challenging issues will assume even more importance in the coming years, since demographic trends are likely to result in greater numbers of the aged, and a greater relative proportion, in the populations of the developed nations. In the USA, the Department of Health and Human Services predicts that by 2030 there will be 71.5 million adults over the age of 65 in the USA, accounting for roughly 20% of the population, in comparison with 36.8 million in 2005 [1].

Epidemiology

Of all age groups, the incidence of both acute symptomatic seizures and unprovoked seizures/epilepsy is highest in people over the age of 65 (Fig. 16.1) [2–4]. The incidence continues to rise with increasing age, and is greatest in the group older than 75 years of age, in which the incidence is five times that of younger adults. Based upon these incidence studies, there are approximately 50 000 new cases of epilepsy in this age group in the USA every year [5].

The overall prevalence of unprovoked seizures is at least 1% in the population over 60 (1.2–1.5% in the population over 75 years), roughly twice the prevalence in younger adults [6,7]. In a study of over one million US veterans at least 65 years of age, 1.8% were found to have epilepsy [8,9]. In specific at-risk populations, such as elderly patients with stroke or dementia, the risk of unprovoked seizures is higher. Overall, stroke patients have an 11.5% probability of experiencing one or more seizures within 5 years of their initial stroke [10]. An elderly patient's risk of an unprovoked seizure increases 6-fold with a diagnosis of Alzheimer's disease and 8-fold with a diagnosis of non-Alzheimer's dementia [11].

Diagnosis

The diagnosis of epilepsy in the elderly is often a challenging process that may be significantly prolonged in many cases. In the Veterans Affairs (VA) cooperative study of seizures in seniors (>60 years old), epilepsy was an initial diagnostic consideration in only 73% of the patients, all of whom were eventually diagnosed with epilepsy [12]. In a subset of this study, looking at 151 veterans, Spitz and colleagues [13] found a significant delay in diagnosis of elderly patients, with a mean time to correct diagnosis of 2.3 years, and a median time of 1 year. Only 37% of patients were correctly diagnosed upon initial evaluation. Of patients with generalized tonic–clonic (GTC) seizures, only two-thirds were diagnosed immediately, and of patients with complex partial seizures, only one-quarter were diagnosed immediately.

The key steps in managing a patient with episodic loss of consciousness (LOC) are:

- determining that the events are in fact seizures and not, for instance, syncope or other causes of episodic LOC;

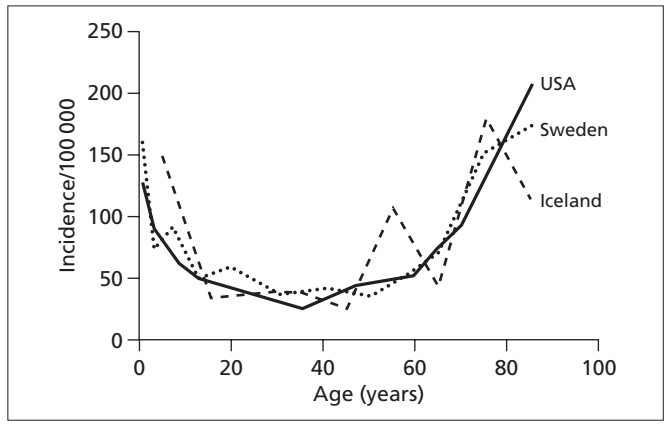

Fig. 16.1 Graph of incidence of unprovoked seizures through lifespan. Reproduced with permission from ref. 4.

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- identifying the aetiology and precipitants for the event, if any;
- determining whether or not the aetiology is amenable to treatment;
- determining the risk of seizure recurrence, and whether or not antiepileptic drug (AED) treatment is needed (acutely and chronically).

There are numerous possible causes of episodic events resembling epileptic seizures (see Chapter 4). These include syncope, transient ischaemic attacks, metabolic disturbances, migraine, transient global amnesia, panic attacks, cataplexy, psychogenic spells, non-specific confusion or amnesia related to dementia, non-epileptic seizures, episodic vertigo and non-specific episodes of dizziness, which may affect up to 10% of older populations [14]. As in younger patients, the most powerful diagnostic tool is an accurate history of the onset, evolution of and recovery from the episode. However, adequate descriptions and eye-witness accounts are often lacking because many older patients may be living alone. In 2006, the US Department of Health and Human Services found that 30% of non-institutionalized people older than 65, totalling more than 10 million people, lived alone [1]. Elderly patients are often brought to the hospital by emergency medical services without anybody to provide a direct description of the episodes. Table 16.1 provides a list of conditions that may commonly mimic seizures and useful clinical features for diagnosis.

In elderly patients, the greatest challenge to a correct diagnosis is the differentiation of seizures from syncopal attacks, as the latter may have multiple causes in older patients, most notably cardiac arrhythmias, carotid sinus syncope and postural hypotension, often due to drugs [15]. Of all the discriminating features, the rapidity of recovery after syncope compared with a seizure is often thought to be the most useful. However, a seizure may be brief (or be reported as brief) whereas syncope associated with an arrhythmia or with prolonged vertical posture may be prolonged. Post-event confusional states are typically prolonged in epileptic seizures and brief with syncope, but may also be prolonged in cerebral anoxia due to syncope associated with a serious cardiac arrhythmia. Cardiogenic or neurocardiogenic (vasovagal) syncope is often accompanied by brief myoclonic jerks, posturing, head turning, automatisms (lip smacking, chewing) or upward deviation of the eyes, and vocalizations may occur [16]. If the anoxic episode itself triggers a full-blown epileptic seizure (a very rare phenomenon, and very difficult to distinguish from an arrhythmia induced by a partial seizure), the situation becomes even more complicated. Typically, syncopal spells are seen infrequently, but in an elderly patient with postural hypotension, this may not be the case. It should be noted that incontinence is not uncommon in syncope, and does not help differentiate syncope from seizures. The most useful features for differentiating seizure from syncope are shown in Table 16.2 [17].

Postictal states are often prolonged in older adults; in one series, 14% of elderly subjects suffered a confusional state lasting more than 24 h, and in some cases it persisted as long as 1 week [18]. When prolonged, the possibility of ongoing seizure activity underlying the 'postictal' states should be suspected, even if the scalp electroencephalogram (EEG) is negative [19]. Postictal hemiparesis (Todd's paresis) is a common occurrence. This may lead to misdiagnosis of stroke; indeed, in one series, this was the most common non-stroke cause of referral to a stroke unit [20]. This is particularly likely to happen when seizures occur against a background of known cerebrovascular disease, and a seizure may be incorrectly diagnosed as a recurrent stroke. In the era of thrombolysis for acute stroke, it is more important than ever to consider the possibility of a seizure rather than stroke, particularly if there is a rapidly improving deficit or if the clinical examination does not fit a known vascular syndrome. One stroke-like presentation that should particularly raise the suspicion of seizures is the occurrence of global aphasia without hemiparesis that resolves (which we have referred to as 'transient global aphasia'), particularly if MRI with diffusion-weighted imaging does not show infarct.

Transient global amnesia (TGA) is a clinical syndrome of the middle-aged or elderly characterized by sudden-onset memory loss without other signs of cognitive impairment or concomitant focal neurological features. During the attack, patients are conscious and alert but show a severe anterograde (and sometimes some retrograde) amnesia. The aetiology of TGA remains debated, and there are proponents of migrainous, epileptic and vascular theories. A report of a 65-year-old woman with recurrent TGA described multiple episodes of amnesia [21]; imaging was normal but an EEG obtained during one of these episodes showed bitemporal asynchronous epileptiform discharges. The episodes were completely controlled by carbamazepine. Thus, TGA (especially if recurrent) can occasionally be a manifestation of a complex partial seizure, although a period with impaired responsiveness is usually present with complex partial seizures (and not in TGA).

Falls, a leading cause for admissions to hospitals, can also be the result of seizures, although these are not usually considered early in the diagnostic evaluation. Often, falls are quickly attributed to cardiovascular causes, gait disturbances, or cerebrovascular events. Even when patients appear encephalopathic, which may be ictal or postictal in nature, the confusional state may be attributed to the associated head trauma and/or associated metabolic disturbances, such as dehydration.

Dementia is a frequent cause of memory loss in the ageing patient. In elderly patients, memory dysfunction may be caused by complex partial seizures and may present either as an insidious fluctuating course of memory loss and confusion that simulates dementia or as discrete episodes of amnesia (and therefore more likely to go unrecognized and unreported). The occurrence of such serial complex partial seizures masquerading as dementia is also known as 'epileptic pseudodementia' and represents a potentially treatable cause of memory dysfunction. When interictal epileptiform discharges (IEDs) are present in patients with epileptic pseudodementia, they have most often been suggestive of a left temporal seizure focus. Tatum *et al.* [22] reported five patients aged 56–79 years who presented to a memory disorders clinic with a prolonged history (1–25 years) of increasingly frequent episodes of memory loss and confusion. Initial EEGs were non-diagnostic in all patients; however, upon repeat EEG (24-h ambulatory in two patients, two video-EEGs and one routine EEG), electrographic seizures (clinically appearing as prominent amnesia), suggesting left temporal origin were

Table 16.1 Common seizure mimics in older adults and useful clinical features for diagnosis.

Diagnosis	Clinical features suggestive of diagnosis rather than seizures
Syncope	Trigger usually identifiable Abrupt onset of autonomic symptoms/pallor No aura or unilateral symptoms LOC < 20 s with rapid return to normal Jerking/posturing, if present, is brief and occurs after the LOC (see also Table 16.2)
Transient ischaemic attack	Variable presentation depending upon area involved Consider focal seizures with any neurological deficit if symptoms are recurrent and stereotyped with no signs of infarct on brain imaging
Migraine (especilally basilar)	Slow march of neurological symptoms over >5 min Prolonged duration (usually 20–60 min) Posterior circulation symptoms; scintillating scotomata; subsequent headache (may be absent)
Transient global amnesia	Prolonged spell (hours) with normal behaviour except for amnesia Personal identity always intact (if not, suspect psychogenic aetiology)
Psychogenic non-epileptic seizures	Psychiatric history (e.g. somatization); history of physical or sexual abuse Eyes closed and normal vitals during spell Recurrent spells not responding to treatment Precipitated by hyperventilation or other suggestive techniques
Panic attack, hyperventilation	Often with environmental trigger; severe fear; hyperventilation with perioral cyanosis, bilateral hand paraesthesias, carpopedal spasm; loss of consciousness absent or incomplete; dyspnoea; palpitations >5 min in duration (seizures are shorter) Associated depression and phobias (95%), esp. agoraphobia; onset in young adulthood
Cataplexy	No loss of consciousness; other features of narcolepsy usually present (daytime somnolence, hypnogogic hallucinations, sleep paralysis) Triggered by emotion, especially laughter
Sleep disorders (paroxysmal nocturnal dystonia, sleep myoclonus, obstructive sleep apnoea, REM behaviour disorder, somnambulism)	Usually difficult to distinguish these from seizures without video-electroencephalographic monitoring, polysomnography, or both, especially if no reliable witness Paroxysmal nocturnal dystonia is probably a CPS/epilepsy in many cases REM behaviour disorder commonly seen in the elderly intermittent loss of REM-related atonia or hypotonia, with abnormal motor activities 'acting out' dreams (often violent) associated with neurodegenerative disease, especially multiple system atrophy and Parkinson's (synucleinopathies) polysomnography for definitive diagnosis treat with clonazepam Somnambulism uncommon in elderly
Staring/behavioural spells in patients with static encephalopathy or dementia	Difficult to distinguish from seizures without video-electroencephalographic monitoring
Metabolic disturbances	Hypoglycaemia Long prodrome; on treatment for diabetes – or insulinoma (rare) Hypo- and hyperglycaemia-related seizures are resistant to AED therapy; treat cause Thyroid storm Typically a history of hyperthyroidism Precipitating event, e.g. infection, surgery, non-compliance with thyroid meds, emotional stress Hypercapnia Subtle personality changes, headache, sedation, confusion More likely to be seen in elderly as ventilatory response to hypercapnia decreases with age Porphyria, acute intermittent Likely precipitant: alcohol, drugs, infection, menstruation Family history is an essential clue for diagnosis
'Drop attacks'	Can be due to cataplexy, cervical spine disease, basilar ischaemia, vertigo attack (Ménière's), seizures (myoclonic, tonic, atonic; rarely complex partial), or syncope (especially cardiac)
Drug intoxication	Prescription medications (antidepressants, antipsychotics, analgesics, anaesthetics, antimicrobials, bronchodilators) Sedative withdrawal (benzodiazepines, barbiturates) may provoke seizures Careful history is important since patients may not have measurable amounts of these drugs in their system at time of seizure occurrence Also consider alcohol withdrawal and substance abuse (cocaine, amphetamines) Low threshold for EEG to different possible NCSE from encephalopathic fluctuations
Infection	Encephalitis HIV (direct infection as well as mass lesions caused by opportunistic infections) Prion diseases (CJD is most common; characterized by rapidly progressive dementia, ataxia and myoclonus (82–100%); periodic discharges on EEG are characteristic)
Epileptic pseudodementia	Serial complex partial seizures mimicking dementia Insidious onset of memory dysfunction and confusion Epileptiform discharges from a left temporal focus may be seen on EEG Treat with AEDs

Adapted and expanded with permission from ref. 17.

AED, antiepileptic drug; CJD, Creutzfeldt–Jakob disease; CPS, complex partial seizure; EEG, electroencephalogram; HIV, human immunodeficiency virus; LOC, loss of consciousness; NCSE, nonconvulsive status epilepticus; REM, rapid eye movement.

Table 16.2 Syncope versus seizure: useful distinguishing features.

	Syncope	Seizure
Before spell		
Trigger (position, emotion, Valsalva)	Common	Rare
Sweating and nausea	Common	Rare
Aura (e.g. smell, déjà vu)	Rare	Common
Unilateral symptoms	Rare	Common
During spell (from eyewitness)		
Pallor	Common	Rare
Cyanosis	Rare	Common
Duration of loss of consciousness	<20 s	>60 s
Movements	A few clonic or myoclonic jerks; brief tonic posturing (a few seconds); duration <15 s; always begin after loss of consciousness	Prolonged tonic phase (~30 s), then prolonged rhythmic clonic movements (~30–60 s); duration >1 min; may begin at onset of loss of consciousness or before; unilateral jerking (partial seizure)
Automatisms	Occasional	Common (in complex partial and secondarily generalized seizures)
Tongue biting, lateral	Rare	Occasional
Frothing/hypersalivation	Rare	Common
Electroencephalography (during event)	Non-specific slowing	Ictal EEG pattern
After spell		
Confusion/disorientation	Rare; <30 s	Common; several minutes or longer
Diffuse myalgias	Rare, brief, usually upper body	Common (hours to days)
CK elevation	Rare	Common (especially after 12–24 h)
Electroencephalography (between events)	Normal	Epileptiform discharges common
Features that are not helpful for differentiating	Incontinence, prolactin level, dizziness, fear, injury other than lateral tongue biting, eye movements (rolling back), brief automatisms, vocalizations, visual or auditory hallucinations	

Adapted with permission from ref. 17.
CK, creatine kinase; EEG, electroencephalogram; GTC, generalized tonic–clonic.

captured in four patients. Four patients improved with AED treatment.

A considerable proportion of patients with seizure-like episodes will actually have non-epileptic events, both physiological and psychogenic. In a study of 94 patients at least 60 years of age (mean 70), referred for video-EEG monitoring for evaluation of paroxysmal episodes, 27 patients were found to have non-epileptic seizures, including 13 with psychogenic non-epileptic seizures (PNESs) [23]. Notably, the majority of those patients diagnosed with non-epileptic episodes had been taking anticonvulsant medications for presumed epileptic seizures. These findings emphasize the need for video-EEG monitoring in patients with atypical events and those whose events have not responded to treatment with AEDs.

Diagnosis becomes increasingly difficult in the presence of co-existing conditions that predispose to syncope. In elderly patients with features suggestive of cerebrovascular disease or of cardiac disease, it may become impossible to ascertain whether or not transient symptoms are cardiac or cerebral in origin. Non-specific abnormalities on an EEG or electrocardiogram (EKG) unrelated to the symptoms may add to the confusion. It has been suggested that head-up tilt testing may be useful in differentiating convulsive syncope from epilepsy [24], and Kenny and Dey [25] extended this to include a carotid sinus massage before and after atropine in prolonged head-up tilt, as cardioneurogenic syncope secondary to carotid sinus hypersensitivity is not uncommon in older people [15]. However, it is crucial to make sure the symptoms precipitated during a tilt table test are typical of habitual spells to avoid false-positive results.

Clinical presentation of epilepsy in the elderly

As would be expected from the range of aetiologies for epilepsy in the elderly, more than 70% of seizures are of partial onset [12,26]. As it is extremely unusual for idiopathic generalized epilepsy syndromes to present in this age group, even apparently generalized tonic–clonic seizures without obvious focal features should be presumed to be partial in onset unless proven otherwise. Seizures in elderly patients may manifest with sensory symptoms, visual phenomena or language disturbances, which may be more difficult to recognize as epileptic in nature. Although it is generally stated that elderly patients have fewer auras and longer durations of postictal confusion, there is little objective evidence to support or refute this. Auras, however, may be very non-specific, for example simply consisting of dizziness. It has been suggested that the variable clinical presentation of seizures in elderly patients is probably because cerebrovascular disease is the most common identifiable cause of new-onset seizures in the elderly, and this tends to most commonly involve the frontal lobe [12]. However, a recent video-EEG monitoring study in elderly patients reported 75% of epileptic events (in 12 patients) as originating from the temporal lobe, similar to young adults [27].

Even after a careful history, examination and appropriate investigations, a firm diagnosis may remain elusive, and in some cases it may be prudent simply to wait and see. A 'therapeutic trial' of anticonvulsants as a diagnostic test is to be recommended even less frequently than in younger patients: unless events are happening very frequently for a therapeutic response to be assessed

quickly, it will rarely produce a decisive answer and only add the burden of unnecessary drug treatment to the patient's problems. Furthermore, if events are occurring frequently, recording them with video-EEGs/EKGs (and ancillary testing as needed, such as blood glucose testing, blood pressure, neurological examination) can provide a definitive diagnosis in almost all cases.

Investigations

Although the importance of a thorough history and comprehensive examination cannot be emphasized enough, routine biochemical and haematological testing may yield helpful clues. Other investigations including electrocardiographic recording, carotid and basilar artery ultrasonography, and orthostatic blood pressure measurement will be directed towards ruling out non-epileptic causes of loss of consciousness; potentially dangerous aetiologies, such as cardiac arrhythmia, should receive first priority, particularly with 'drop attacks' or unwitnessed and unexplained falls. Often, even after extensive cerebral and cardiovascular investigation, the clinician will remain uncertain whether the patient's episodes are cerebral or cardiac in origin, unless a typical spell is recorded with simultaneous video-EEG and electrocardiographic monitoring.

Electroencephalography

The value of special investigations, in particular electroencephalography and neuroimaging, is sometimes overestimated. Misinterpretation of EEG findings or over-reliance on the EEG frequently contributes to misdiagnosis [28]. The presence or absence of interictal epileptiform discharges (IEDs) on EEGs is not definitive and may be misleading [29]. Interictal EEG findings typically change with age [30]. It is commonly stated that epileptiform discharges are less frequently seen in elderly patients with seizures [31,32]. However, the results of at least two monitoring studies using video-electroencephalography in elderly patients appear to suggest otherwise. Kawai *et al*. reviewed the video-EEG records of 71 geriatric veterans (average age of 68 years). Twelve patients had epileptic seizures recorded. Ten of those 12 patients with definite seizures had focal interictal epileptiform discharges, including nine out of nine with temporal lobe seizures. Similarly, in a series of 94 patients (≥60 years) who underwent monitoring using video-EEG [23], 76% of the 46 patients with epileptic events captured on video-EEGs had IEDs, and 26% of the patients with non-epileptic events had 'interictal' discharges as well. These findings reinforce the importance of recording typical spells with video-EEG monitoring, as interictal recordings alone appear to be inadequate for diagnosis in this age group.

When EEGs are interpreted by physicians without specialized training, a number of benign or normal patterns can be commonly misinterpreted as epileptiform. One study identified 46 patients referred to an epilepsy centre with a previous diagnosis of epilepsy; a prior EEG available for all these patients showed wicket patterns. Upon 'blinded' re-interpretation by electroencephalographers at the epilepsy centre, it was found that 46% (21 out of 46) of the patients with wicket patterns also had epileptogenic patterns on the previously performed EEGs or had seizures confirmed with prolonged video-EEG monitoring, while the remaining 54% (25 out of 46) of patients had only wicket rhythms (but no true spikes or sharp waves) that were erroneously diagnosed as epilepsy [33]. Benbadis *et al*. [34] reported 15 patients who were eventually diagnosed with psychogenic non-epileptic seizures, but had previously carried a diagnosis of epilepsy based on EEGs misinterpreted as epileptiform [34]. Of the 15 records reviewed, the patterns that were incorrectly considered epileptiform were wicket spikes ($n = 1$), hypnogogic hypersynchrony ($n = 1$) and hyperventilation-induced slowing ($n = 1$). In the other 12 records, simple fluctuations of sharply contoured baseline background activity and fragmented alpha activity, not identifiable specific variants, were misinterpreted as epileptiform. Repeating the EEG or having it re-interpreted at a tertiary epilepsy centre by a certified electroencephalographer can be helpful in problematic cases. A routine EEG may *support* the diagnosis of epilepsy, especially if clear-cut epileptogenic or ictal discharges are observed, but it is important to remember that a normal EEG is perfectly consistent with epilepsy and can never rule it out. The range of 'normal' increases with age, so that discriminating normal from abnormal becomes more difficult and non-specific or unrelated abnormalities are commonly seen in older patients [35].

Neuroimaging

The mainstay of neuroimaging in epilepsy is MRI (magnetic resonance imaging), and its value in people with epilepsy has been amply demonstrated [36]. This particularly holds true for patients with medically refractory partial seizures, for whom appropriate surgical treatment results in complete resolution of seizures in the majority of patients with unilateral mesial temporal lobe epilepsy [37] or tumours [38], and even dual pathology [39].

Given the lack of prospective data regarding the diagnostic yield of neuroimaging in elderly patients with seizures, as a general rule all patients with new-onset seizures regardless of age at onset need to undergo appropriate imaging to rule out stroke, neoplasms, and subdural haematomas among other causes, and proceed with management accordingly.

Risk of recurrence

In all patients presenting with a first unprovoked seizure, the long-term (at least 2 years' follow-up) risk of recurrence is about 38%, ranging from 25% to 52% [40–43]. Prognostic factors which clearly increase the risk of seizure recurrence include abnormal EEG findings (particularly epileptiform) and the presence of an underlying recognized aetiology (i.e. remote symptomatic seizure).

Data on risk of recurrence after the first unprovoked seizure in older patients are largely inconclusive, as large-scale studies are lacking. However, in the presence of a recognized underlying neurological condition to which the seizure can be attributed, the risk of recurrence is roughly double that of a cryptogenic first seizure [41]. In selected populations, the recurrence rate may be very high, as Luhdorf and colleagues [32] found that seizures recurred in more than 80% of a small series of patients with a remote history of stroke. In many or most cases, a careful history will reveal that the presenting seizure is not actually the first seizure [44].

As many newly diagnosed unprovoked seizures in the elderly have an antecedent cause, most often cerebrovascular disease, it

is likely that most newly diagnosed seizures in the elderly population are likely to recur. In the elderly population, it is reasonable to begin anticonvulsant medication after the first unprovoked seizure, even in the absence of underlying demonstrable pathology. However, useful prospective data are lacking to confirm or refute the clinical value of this approach. In making the decision to begin pharmacological treatment, seizure severity, the risk of recurrence, personal preference and the need to drive must be weighed against the potential for adverse effects of AEDs, which, as discussed, may be more of a concern in elderly patients.

Treatment of epilepsy in the elderly

Although it has been frequently stated that epilepsy is more easily controlled in the elderly population [45,46], there is a dearth of large studies specifically addressing this issue. Data from the two recent studies addressing tolerability of anticonvulsants in the elderly showed seizure-free rates that were not very different from those of the general adult population. Brodie and colleagues compared carbamazepine and lamotrigine in a randomized trial of 150 elderly patients, in whom only 33% remained seizure free during the final 16 weeks of the study [47]. Although a high rate of medication withdrawal probably contributed to the relatively low rate of seizure freedom, these findings suggest that seizures are not so easily controlled in this population. Similarly, in the VA cooperative study #428, which randomized elderly patients with new or recent-onset epilepsy to treatment with gabapentin, lamotrigine or carbamazepine, 53% of patients who remained on treatment were seizure free at 12 months [48]. These data are not substantially different from seizure control rates in the general population; for instance, in a study of 470 previously untreated patients with epilepsy, aged 9–93, Kwan and Brodie [49] found that 47% became seizure free on the first drug, and a total of 67% became seizure free with the second or third monotherapy agent.

Pharmacokinetic changes

When choosing an AED, and when determining the dosing regimen for an elderly patient, one must be cognizant of the high risk of age-related physiological changes. This does not imply that elderly people with epilepsy are a homogeneous group characterized by similar specific physiological changes that will predictably affect the choice of drug and dosage. It should also be noted that the degree and rates of 'age-related' change are not reliably predictable across this age group; a great degree of variability is seen even within normal healthy individuals, and even more variability occurs in elderly patients, who often have multiple co-morbid conditions [8]. Other factors that will contribute in varying degrees to pharmacokinetic variability include physical frailty, dietary influences, compliance and drug interactions resulting from multiple co-medications [50,51]. Nevertheless, the major goal of seizure management in old age is the same as in younger patients: seizure control with minimal side-effects.

A description of pharmacokinetic properties and known age-related changes follows below. See Table 16.3 for a summary of the pharmacokinetic properties of the AEDs.

Absorption

Absorption of medications depends upon the dissolution of drug formulation, largely dependent upon gastric acid secretion, which often declines in the elderly [52]. In addition, gastric emptying may slow, intestinal transit time may increase, mesenteric blood flow may decrease, and the intestinal absorptive surface may decrease, all contributing in varying degrees to variable absorption of different drugs. Overall, this combination of factors typically results in the diminished ability to absorb AEDs, thus reducing bioavailability. This may be compounded by the frequent use of antacids in the elderly, which can specifically impair the absorption of phenytoin [53]. In addition, gabapentin, which is absorbed via a saturable L-amino acid transmitter system in the small intestine [54], may be particularly susceptible to physiological changes in gastrointestinal absorption.

Protein binding

Elderly patients are at significant risk for acute systemic and neurological illnesses, many of which may cause a significant decline in serum albumin levels. Suboptimal nutrition may also contribute to lower albumin levels. A reduction in serum albumin concentrations will cause the free fraction of highly protein-bound medications to increase substantially, and may result in prominent adverse effects despite little or no change in the total serum level. AEDS that are highly protein bound include tiagabine, phenytoin, valproate, diazepam, clonazepam, clobazam and, to a lesser extent, carbamazepine [55].

Hepatic clearance

Hepatic mass and blood flow both decline with age, such that liver volume is about 25% lower in people age 65 than in young adults [56]. The majority of drugs metabolized in the liver are metabolized by the cytochrome P450 system, and with increasing age this system declines in efficiency, although to a variable, unpredictable degree [57].

The AEDs that are metabolized primarily by the cytochrome P450 system include carbamazepine, ethosuximide, oxcarbazepine, phenytoin, phenobarbital, primidone, tiagabine and zonisamide. Felbamate, topiramate and valproate are also partially metabolized via this pathway [8].

The hepatic glucuronidation conjugation process is believed to decline much less with age. AEDs primarily undergoing conjugation include lamotrigine, valproate and the active metabolite of oxcarbazepine [8].

Renal clearance

The most consistent change with age is an age-related decline in renal function, associated with reduction in renal mass, loss of glomeruli, resulting in reduced glomerular filtration rate (GFR) and a reduced ability to handle renally excreted medications and toxins. GFR declines on average by about 50% between the third and eighth decades of life [58], but the degree of change is highly variable, with about one-third of patients not experiencing significant decline [59]. Because muscle mass, the source of serum

Table 16.3 Pharmacokinetic properties of commonly used AEDs in adults.

AED	Oral bioavailability (%)	Plasma protein binding (%)	Half-life (h): patients not on EIAEDs	Half-life (h): patients on EIAEDs	Main route of elimination
Carbamazepine	≤85	~80%	10–25	5–12	Hepatic epoxidation, then conjugation (the 10,11-epoxide metabolite may contribute to efficacy)
Felbamate	~90	~30	14–23	10–20	Hepatic hydroxylation and then conjugation; 40% renal excretion
Gabapentin	≤60 (decreases with increasing dose)	0	5–7	5–7	Renal excretion
Lamotrigine	100	~55	15–30 (30–90 when co-medication is valproate)	8–20 (15–60 when valproate is also present)	Hepatic glucuronidation
Levetiracetam	~100	0	6–8	5–8	Partially hydrolysed to inactive compound; mostly renal excretion
Oxcarbazepine	>95 (active metabolite is MHD)	~40 (MHD)	8–15 (MHD)	7–12 (MHD)	Ketoreduction to MHD, which is eliminated via hydroxylation and then glucuronide conjugation
Phenobarbital	100	45–60	75–125	75–125	Oxidation, conjugation and renal excretion
Phenytoin	~95	85–95	7–42 (increases with increasing dosage)	7–42 (increases with increasing dosage)	Hepatic oxidation and hydroxylation then conjugation
Pregabalin	~90	0	5–7	5–7	Renal excretion
Tiagabine	~100	96	4–13	4–5	Hepatic oxidation then conjugation
Topiramate	>80	~20	20–30	10–15	Mainly hepatic oxidation, and renal excretion
Valproic acid	~100	85–95	10–20	6–12	Hepatic glucuronidation and oxidation then conjugation
Vigabatrin	60–70	0	5–8	5–8	Renal excretion
Zonisamide	≥65	50	50–70	25–35	Hepatic acetylation, isoxazole ring cleavage (via CYP3A) then glucuronide conjugation and renal excretion

AED, antiepileptic drug; CYP3A, cytochrome P450, family 3, subfamily A; EIAED, enzyme-inducing antiepileptic drug (these include carbamazepine, phenytoin, phenobarbital and primidone); MHD, 10-monohydroxy metabolite.

Table 16.4 Average changes in apparent oral clearance of older and newer AEDs in elderly patients.

AED	Decrease in drug clearance in elderly compared with young adults (%)	Reference
Carbamazepine	25–40	Battino *et al*. (2003)
Felbamate	10–20	Richens *et al*. (1997)
Gabapentin	~30–50	Boyd *et al*. (1999)
Lamotrigine	~35	Posner *et al*. (1991)
Levetiracetam	~20–40	Patsalos (2004), Hirsch *et al*. (2007)
Oxcarbazepine	~25–35[a]	van Heiningen *et al*. (1991)
Phenobarbital	~20	Messina *et al*. (2005)
Phenytoin	~25[b]	Bachmann and Belloto (1999)
Tiagabine	~30	Snel *et al*. (1997)
Topiramate	~20	Doose *et al*. (1998)
Valproic acid	~40[c]	Perucca *et al*. (1984)
Vigabatrin	~50–85[d]	Haegele *et al*. (1988)
Zonisamide	No data	–

Modified with permission from ref. 8.
Interindividual variation may be considerable in relation to age and other factors.
[a] Data refer to the active metabolite monohydroxycarbazepine.
[b] Decrease in clearance of unbound drug may be greater.
[c] Decrease in unbound drug clearance. Clearance of total (unbound + protein bound drug) may not change.
[d] These patients, who had various pathologies, were preselected to cover a wide range of impaired renal function.

creatinine, declines with age, the serum creatinine level often does not decline in parallel with declining GFR.

The AEDs that are primarily renally excreted include gabapentin, levetiracetam, vigabatrin and pregabalin. Felbamate, zonisamide, and topiramate are also partially renally excreted [55]. Table 16.4 summarizes the literature on age-related changes in the clearance of the commonly used AEDs [8].

Pharmacodynamic changes

In addition to the pharmacokinetic effects potentially altering levels of medication in the serum, it is also likely that pharmacodynamic alterations in the effects of the drugs at the cellular level are important in the elderly. In particular, adverse central nervous system effects often occur at serum free levels that do not typically produce adverse effects in younger adults. As a result, the therapeutic window, between efficacy and toxicity, is often narrower for AEDs in the elderly population (Fig. 16.2) [60].

Antiepileptic drug choice

As virtually all of the currently used AEDs have been shown to be of approximately equal efficacy in the treatment of partial-onset seizures, considerations of tolerability and safety, including

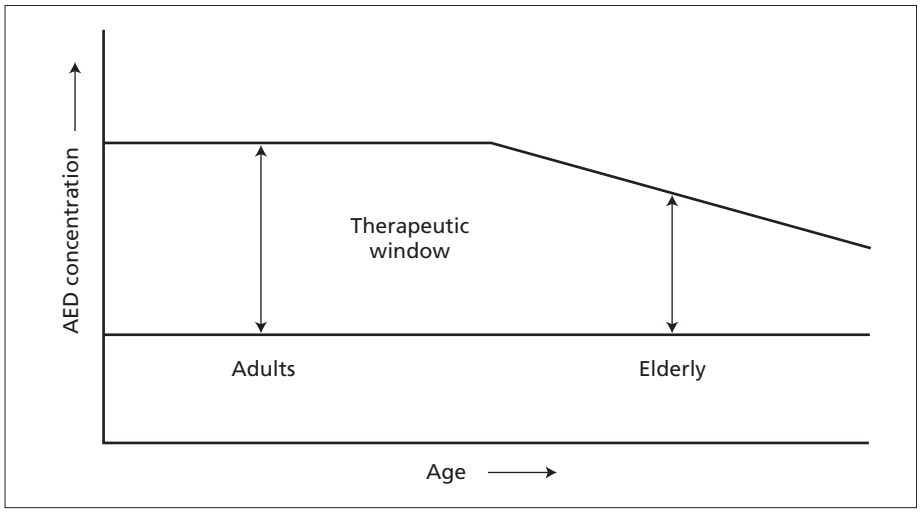

Fig. 16.2 Effect of age on therapeutic ranges. The elderly typically have a narrow therapeutic window, the range between the lowest effective concentration and the maximal tolerated concentration. Reproduced with permission from ref. 61.

Table 16.5 Desirable features of an antiepileptic drug for use in the elderly.

No interactions with other medications
No interactions with other AEDs
Can be introduced at therapeutic doses
No metabolism
No protein binding
Once- or twice-daily dosing
Laboratory monitoring not necessary
Excellent safety record
Good side-effect profile
High therapeutic index
Little effect on cognitive function
Psychoactive benefits

Reproduced with permission from ref. 60.

pharmacokinetics and the potential for drug interactions, are at least as important as efficacy in the selection of an AED (Table 16.5) [60].

Older antiepileptic drugs

Although the older AEDs (including phenytoin, phenobarbital, primidone, valproate and carbamazepine) are effective in partial epilepsy [61,62], several features make them less than ideal choices. Phenobarbital and primidone are particularly sedating and may significantly depress cognition, and were shown to be significantly less well tolerated than carbamazepine and phenytoin in the first VA cooperative trial (including all ages) [62]. In addition, these medications are potent hepatic enzyme inducers, reducing the efficacy of many commonly used medications, and are also likely to contribute to bone loss. With these effects in mind, these AEDs should not be considered first-line (and probably not second-line) medication choices in this population.

Phenytoin, despite being the most widely prescribed AED in the USA, has many troublesome features. In particular, the transition from first- to zero-order kinetics at modest doses often leads to widely variable serum levels with small changes in dosing, resulting in a high risk of toxicity. It has adverse effects, including imbalance and ataxic gait, at modest levels and can result in an increased risk of falls and consequent fractures. Because of its potent hepatic enzyme-inducing properties and high degree of protein binding, medication interactions are prominent. It has been clearly demonstrated that even 1 year of use in monotherapy leads to measurable loss of bone density [63]. Although we believe that phenytoin should no longer be used as a first-line (nor probably second-line) agent in the elderly, prescribing patterns are not likely to change markedly in the near future. When phenytoin must be used, dosage adjustments should be made in small increments of 30 mg in order to minimize risks of toxicity. We also recommend not changing formulations of phenytoin (e.g. not changing from brand to generic, or from one generic to another) without close monitoring of serum levels.

Valproate is a potent inhibitor of hepatic enzymes, is highly protein bound and can be involved in numerous drug interactions. Valproate encephalopathy can rarely result from hyperammonaemia in the absence of hepatic enzyme abnormalities [64], and this should be considered in any patient on valproate with unexplained encephalopathy. In addition, it is not rare for valproate to exacerbate or cause parkinsonism [65]. Nonetheless, valproate is often well tolerated and effective in older adults.

In a retrospective analysis of 417 older adults (≥55 years old) from the Columbia AED Database, we compared 12-month retention (a composite measure of efficacy and tolerability) in 247 older adults newly started on any AED at our centre over a 4-year period. The average 12-month retention rate was 65%. Without controlling for severity, lamotrigine had the highest 12-month retention rate (78.6%; n=126), which was higher ($P < 0.05$) than the 12-month retention rates seen with carbamazepine (48.4%; n=31), gabapentin (59%; n=39), oxcarbazepine (23.5%; n=34), phenytoin (59.3%; n=27) and topiramate (55.6%, n=18). The second highest retention rate was seen with levetiracetam (72.5%; n=102), which was statistically higher than with carbamazepine (48.4%) and oxcarbazepine (23.5%). Oxcarbazepine had the worst retention rate (23.5%; n=34), which was significantly lower than with all other AEDs. When the results were stratified into non-refractory and refractory patients, relative rates remained comparable. The 12-month retention rate for valproate in the refractory group was 90% (n=10). In the same analysis, the 12-month seizure freedom rate for valproate in the overall group was only 27.8%, so it may be likely that the high retention rate seen with valproate is attributable, at least in part, to good tolerability of valproate [66].

Carbamazepine, also widely prescribed, has a less than favourable pharmacokinetic profile. As an inducer of hepatic enzymes, numerous drug interactions can occur. Hyponatraemia occurs more commonly in elderly patients taking carbamazepine [67]. Carbamazepine has been shown to be less well tolerated than many of the newer AEDs (see below).

Newer antiepileptic drugs

Two prospective trials in the elderly have shown that lamotrigine and gabapentin are better tolerated and thereby more effective than carbamazepine.

In the VA cooperative study #428, patients 60 years of age or older with newly diagnosed epilepsy were randomized to treatment with gabapentin 1500 mg per day, lamotrigine 150 mg per day or carbamazepine 600 mg per day; dose adjustments were permitted [48]. The primary outcome measure of the study was early termination, which occurred in 64.5% of patients taking carbamazepine, a rate that was significantly higher than the 51% of patients taking gabapentin ($P = 0.008$) and 44% of patients taking lamotrigine ($P < 0.0001$). Fewer lamotrigine patients terminated the study because of adverse reactions than either carbamazepine ($P < 0.0001$) or gabapentin ($P = 0.015$) patients. There were no significant differences in seizure-free rates or time to first seizure. For all three AEDs, the primary factor resulting in early termination was the occurrence of adverse effects: there were significantly more early terminators on carbamazepine (31%) compared with lamotrigine (12.1%; $P < 0.0001$) and on gabapentin (21.6%) compared with lamotrigine (12.1%; $P = 0.015$). The most common neurotoxic side-effects in all three treatment groups included sedation, cognitive disturbances, dizziness, gait problems and changes in mood/affect. More patients on gabapentin experienced large weight gain (>18 pounds) than on carbamazepine ($P = 0.005$) or lamotrigine ($P = 0.014$). Water retention was significantly more likely with gabapentin than with carbamazepine ($P = 0.004$) or lamotrigine ($P = 0.02$). More patients lost weight with lamotrigine than with gabapentin ($P = 0.002$). Hypersensitivity (rash of any degree) occurred more frequently with carbamazepine than with lamotrigine ($P = 0.007$). Of seven patients hospitalized for hypersensitivity reaction, six were in the carbamazepine group and one was treated with lamotrigine. Hyponatraemia (sodium less than 130 mg) occurred more frequently in patients on carbamazepine than on gabapentin.

A similar earlier study by Brodie and colleagues [47], randomizing 150 newly diagnosed elderly subjects (mean age 77 years) with epilepsy to lamotrigine (median dose 100 mg/day) or carbamazepine (400 mg/day), found that 42% of patients on carbamazepine dropped out because of adverse events as opposed to only 18% of patients on lamotrigine [47]. Notably, 29% of patients on carbamazepine complained of somnolence in contrast with only 12% of patients on lamotrigine. Also of interest, only 3% of patients on lamotrigine developed allergic rash, as opposed to 19% on carbamazepine.

The newer AEDs have been reviewed extensively in the 2004 American Academy of Neurology (AAN) guidelines on the efficacy and tolerability of the new antiepileptic drugs [68,69]. Overall, lamotrigine has been shown to have a favourable adverse effect profile. It is non-sedating, and does not produce significant cognitive dysfunction. It is not an inducer of hepatic enzymes and is not highly protein bound, resulting in minimal drug interactions. It should be noted that enzyme-inducing medications and hormone replacement may significantly reduce its level. The interaction between lamotrigine and valproate is a complicating factor, and co-medication with valproate may increase lamotrigine levels by two- to threefold. One potential negative aspect of therapy with lamotrigine is the need for slow titration because of the risk of a potentially severe allergic reaction if titration is too rapid. With gradual dosage titration according to the guidelines, this risk is no greater than (and potentially less than) the risk with most of the older AEDs.

Levetiracetam, approved by the US Food and Drug Administration (FDA) after the VA study began, also has favourable features. It does not produce significant cognitive dysfunction, is renally excreted, is not highly protein bound, and does not undergo oxidative metabolism in the liver; thus it is not associated with any major pharmacokinetic interactions [70]. Enzyme-inducing AEDs, however, can moderately decrease serum levetiracetam concentrations [71–73] but the clinical significance of this decrease is still unclear. A small but significant percentage of patients experience irritability, depression or other behavioural side-effects. A great benefit of levetiracetam is that it has therapeutic efficacy at starting doses; the odds of becoming seizure free increase over twofold as early as the first day of adjunctive treatment with levetiracetam at doses of 1000 mg/day, in patients with refractory epilepsy [74].

Gabapentin and pregabalin also have favourable profiles. Both are renally excreted, have minimal cognitive effects, are not hepatic inducers, and are not protein bound. In addition, both probably have therapeutic efficacy at starting doses.

Oxcarbazepine, although hepatically metabolized, is a weak inducer of hepatic enzymes, and has minimal drug interactions. As is the case with carbamazepine, hyponatraemia is seen more often in elderly patients, and is even more frequent with oxcarbazepine than carbamazepine. Hyponatraemia is particularly common in older adults on diuretics or selective serotonin reuptake inhibitors (SSRIs) [75].

Zonisamide and topiramate are often well tolerated, but both seem to be associated with a relatively high incidence of sedative and cognitive adverse effects. Each is partially excreted unchanged via renal mechanisms and partially metabolized in the liver. Neither is a hepatic enzyme inducer, nor are they highly protein bound, and there are few drug interactions. Each should be titrated slowly. It should also be noted that both are weak carbonic anhydrase inhibitors and carry a small risk of renal stones.

In a recent study of 20 558 veterans with epilepsy aged 65 or older, 70% were found to be on phenytoin [8,76]. An additional 17% were on phenobarbital, 10% on carbamazepine, and notably, gabapentin and lamotrigine were used in less than 10% of newly diagnosed cases.

In a survey of experts, 'opinion leaders in the field of epilepsy' in 2005, for treatment of localization-related epilepsy (LRE) in the healthy elderly, lamotrigine was selected to be the treatment of choice in 66%, recognized as first line by 98%. Levetiracetam was also selected as first line by 95%. Gabapentin, carbamazepine and oxcarbazepine were also recognized as first-line agents by 71%, 59% and 61%, respectively. Other agents were selected

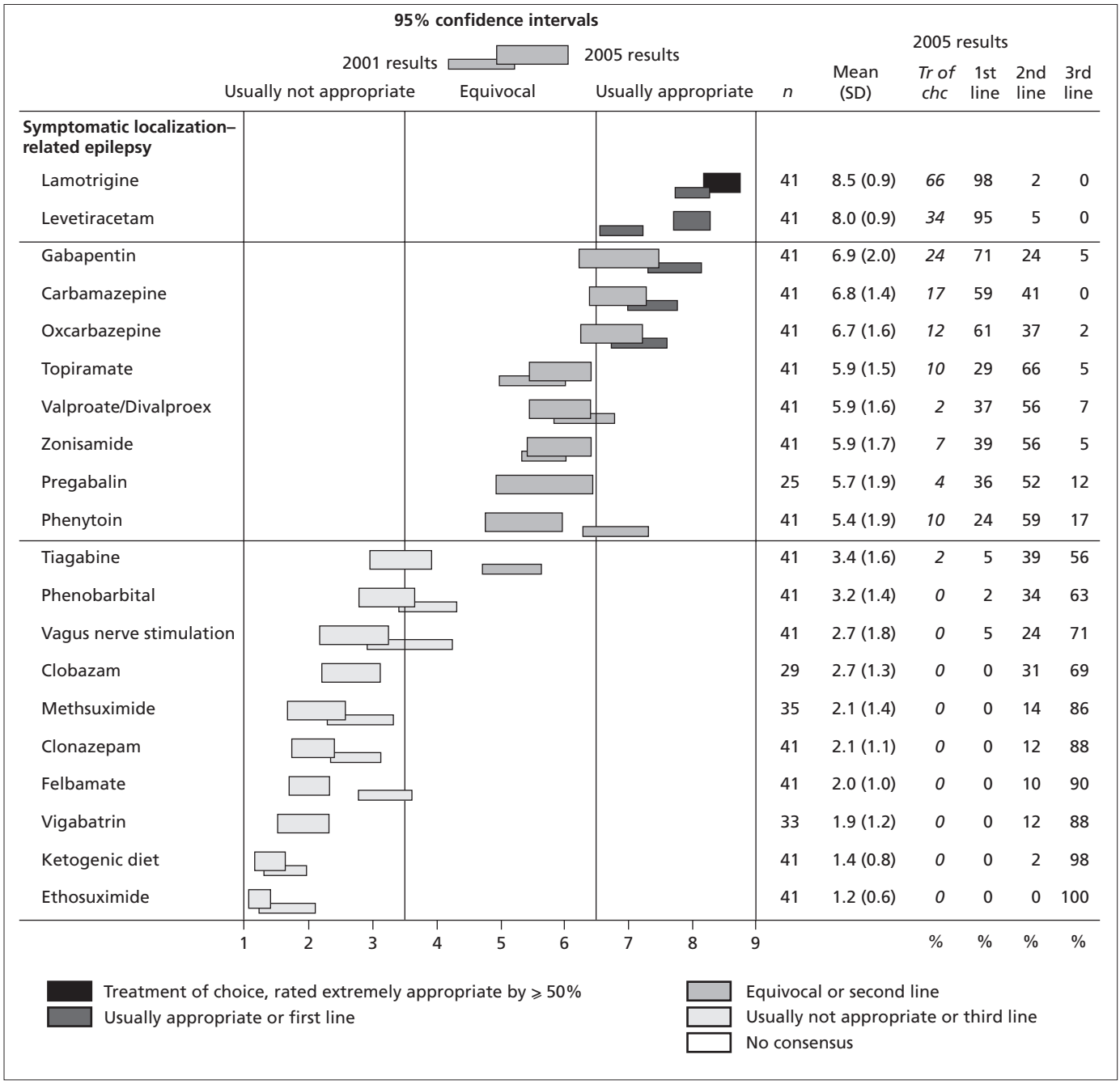

Fig. 16.3 Antiepileptic drug therapy for elderly patients with symptomatic localization-related epilepsy. In this scenario, assume that the patient is a medically stable elderly man or woman. Please rate the appropriateness of each of the following therapies as they might be used in monotherapy in this population. Keep in mind the epilepsy syndrome diagnosis. Reproduced with permission from ref. 77.

by far fewer experts. Phenytoin was selected as first line by only 24% and phenobarbital by only 2% (Fig. 16.3) [77].

Co-morbid conditions and medication interactions

Given the frequency of co-morbid conditions in the elderly, and the myriad of medications used to treat these, these issues must be at the forefront when selecting an AED. Nearly 90% of elderly patients in the community take at least one prescription medication [78], and nursing home residents take an average of approximately five routine medications [53]. An attempt should be made to tailor the expected side-effect profile of the AED to the characteristics of the individual: for example, a drug causing weight loss may be a good choice for the obese patient. Table 16.6 compares AEDs that may be more or less appropriate based on specific co-morbid conditions.

Table 16.6 Selection of AEDs based on common co-morbid conditions: examples.

Co-morbid condition	Potentially beneficial for co-morbid condition	Potentially harmful for co-morbid condition
Osteoporosis	–	Phenobarbital, phenytoin
Obesity	Topiramate, zonisamide	Valproate > gabapentin, pregabalin
Depression	Lamotrigine	Levetiracetam, phenobarbital
Anxiety	Gabapentin, pregabalin	Levetiracetam
Bipolar disorder	Carbamazepine, lamotrigine, valproate	–
Cognitive problems/ dementia		Topiramate
Headache/migraine	Topiramate, valproate	–
RLS/PLMS	Gabapentin	–
Renal stones	–	Topiramate, zonisamide
Hyponatraemia	–	Oxcarbazepine > carbamazepine
Multiple or severe prior allergy/rash	–	Carbamazepine, lamotrigine, phenytoin > oxcarbazepine, phenobarbital, zonisamide

PLMS, periodic limb movements in sleep; RLS, restless legs syndrome.

The major interactions are based upon the cytochrome P450 enzyme-inducing or -inhibiting effects of the AEDs. Potent hepatic inducers include phenobarbital, phenytoin, carbamazepine and phenytoin. Felbamate, oxcarbazepine and topiramate are mild hepatic inducers. Valproate is a potent hepatic enzymatic inhibitor. Ethosuximide, gabapentin, lamotrigine, levetiracetam, tiagabine, zonisamide and pregabalin are neither inducers nor inhibitors of hepatic enzymes. Patsalos and Perucca have published an extensive review on the topic, and readers are referred here for further detail [79]. In summary, lamotrigine, levetiracetam, gabapentin, pregabalin, zonisamide and topiramate have the lowest potential for interaction with medications used to treat co-morbid conditions in the elderly.

In addition, commonly used medications in the elderly may also affect the levels of certain AEDs, and these have also been summarized in the Patsalos and Perucca review. Several commonly used medications inhibit the cytochrome P450 enzymes, and consequently may increase the levels of AEDs metabolized via this pathway. These include H2-blockers (cimetidine), macrolide antibiotics (erythromycin, clarithromycin), antifungal agents (ketoconazole, fluconazole) and isoniazid. Ticlopidine has also been found to increase levels of carbamazepine and phenytoin. Rifampin is an enzyme inducer and can lead to loss of efficacy of many AEDs.

Epilepsy surgery

Given the challenges associated with AED selection and treatment of epilepsy in the elderly, resective surgery must be considered in suitable cases. However, few studies have assessed the efficacy of surgery for temporal lobe epilepsy (TLE) in the elderly [80–83]. In a retrospective study [84], 52 patients >50 years old were studied who underwent surgical treatment for refractory mesial TLE (mean duration of epilepsy, 33 years; mean age at surgery, 55 years). Forty selective amygdalohippocampectomies (33 for hippocampal sclerosis, seven for removal of a mesiotemporal lesion), five lateral temporal lesionectomies plus amygdalohippocampectomy and seven anterior temporal lobectomies were performed. The outcomes were compared with a control group of 321 patients who were younger than 50 years of age at surgery. In the older group, 37 patients attained complete seizure control (71% Engel class I compared with 72% class I in younger patients) and 10 patients had only rare postoperative seizures (19% class II). Four patients improved more than 75% (8% class III), and one patient did not improve (2% class IV). A subgroup analysis of 11 patients older than 60 years at surgery showed a similar rate of seizure control. A trend towards better seizure control was noted in 16 patients with an epilepsy duration of <30 years (all class I or II), and in 20 patients with a seizure frequency of fewer than five seizures per month (all class I or II). A 3.8% rate of permanent neurological morbidity (dysphasia and hemiparesis) was noted. Neuropsychological testing revealed low preoperative performances and some gradual further deterioration after surgery. In the older group, postoperative attentional performance improved significantly in 11 patients (32.4%), remained unchanged in 14 patients (41.2%), and deteriorated significantly in nine patients (26.5%). Younger patients showed significantly stronger benefits after surgery regarding postoperative attentional performance ($P = 0.016$). These results suggest that many elderly patients may benefit significantly from epilepsy surgery, despite a prolonged history of seizures.

The impact of seizures in old age

Seizures in an elderly person can have profound physical and psychological consequences. The physical disability is caused, at least partly, by the increased incidence of falls and diminished bone health in the elderly population, with the consequential increased risk for serious fractures in this age group. The additional risk of falls conferred by seizures, along with the potential deleterious effects of AEDs on bone health, creates a dangerous potential for fractures in elderly patients with epilepsy. Although no adequate prospective studies have been undertaken, there are data to suggest (as reviewed by Downton *et al.* [85]) that a fall may mark a watershed in an older patient's life, after which there is a sharp decline in functional independence that can be attributed not only to the disease underlying the fall but also to a loss of self-confidence.

In a study of more than 8000 community-dwelling women older than 65 years, those taking AEDs were 75% more likely to experience a fall than those not taking AEDs [86]. This increase is likely to be partly related to seizures but also to an increased sensitivity to the CNS effects of AEDs in older patients resulting in a greater tendency to imbalance and consequent falls. Patients with epilepsy have been shown to have approximately double the fracture risk of control subjects [87].

In adults, bone mineral density (BMD) peaks between the ages of 20 and 30 years. Thereafter, BMD steadily and gradually continues to decline, and this is more pronounced in women

following the onset of menopause. Some commonly used older AEDs that are potent inducers of the cytochrome P450 enzyme system are associated with altered bone metabolism and decreased bone density; these include phenytoin, carbamazepine, primidone and phenobarbital [88]. A recent longitudinal study of 93 premenopausal women (age 18–40 years) receiving a single AED (either carbamazepine, lamotrigine, phenytoin or valproate) showed that young women treated with phenytoin monotherapy had significantly more bone loss at the femoral neck (2.6%) over 1 year of treatment than women treated with the other AEDs [63].

Valproate, an inhibitor of the P450 system, was initially believed not to affect bone health, but was recently found to be associated with reductions in BMD [89,90]. Polytherapy has been shown to be associated with a higher risk of bone metabolism abnormalities than monotherapy [91]. Multiple mechanisms have been postulated to support the association; however, no single mechanism explains all the findings.

Data regarding lamotrigine's effects on bone health are mixed. One study linked exposure to lamotrigine to short stature in children, which the investigators speculated as having been possibly related to less physical activity in this group [92]. Another prospective study found elevated osteocalcin, a marker of bone formation, in association with lamotrigine treatment [93]. In contrast, premenopausal women treated with lamotrigine did not have significant reductions in BMD or changes in bone turnover markers [94].

The effects of topiramate and zonisamide on bone have received limited study. The carbonic anhydrase inhibitor action of these AEDs, resulting in renal acidosis, may have secondary negative effects on bone. Interestingly though, carbonic anhydrase also potentiates the action of osteoclasts and so, theoretically, inhibitors may have a bone-sparing effect. The findings of a study in women with glaucoma treated with acetazolamide (another carbonic anhydrase inhibitor) appear to support this hypothesis [95]. Another randomized preliminary study of topiramate as treatment for obesity did not find significant changes in bone turnover markers compared with placebo-treated control subjects [96]. There are limited data about levetiracetam's effects on bone: a preliminary study with a limited sample size found no effects [97].

A number of neuropsychological and neuroimaging studies have linked the deterioration of specific cognitive functions (e.g. memory) and general intellectual ability (IQ) to both temporal and extratemporal epilepsy and to disease variables such as early age at onset and seizure frequency [98,99]. Patients with chronic epilepsy have up-regulation of amyloid precursor protein, increased rates of senile plaque formation and premature accumulation of corpora amylacea; there is increasing evidence that the presence of the *apoE-e4* allele in patients with chronic TLE is linked to age-accelerated memory impairment [100,101]. This literature has been recently reviewed by Hermann and colleagues [100]. Two population-based studies of medical co-morbidities (from the UK and Canada) showed a significant association between Alzheimer's disease and other dementias in persons with epilepsy compared with control subjects [103,104]. Breteler *et al.* [105] demonstrated an age-accelerated risk of dementia in 4505 patients (aged 50–75 years) with epilepsy, compared with age-matched subjects with other medical disorders, over an 8-year observation period [105].

Lifestyle factors, such as decreased physical and mental activity and lack of a social network, are also risk factors for cognitive decline in later life [106]. Many of these risk factors are more common in patients with epilepsy. It is therefore important not only to study causality of these individual risk factors and subsequent cognitive decline but also to ascertain whether cumulative exposure to these risk factors in younger years increases the risk of adverse cognitive outcomes in later life. For many patients, cognitive decline is as important a factor in determining quality of life as seizure control.

Falls in seizures can have a marked psychological impact. Falls can create a greater degree of stigmatization, affect interactions with others, including friends, relatives and caregivers, and restrict activity, mobility and independence (for example by losing a driver's licence), limit participation in decision-making processes and increase dependency. In summary, older patients may experience considerable marginalization and disempowerment, and although seizures will not affect employment or education as in younger persons, the impact on interpersonal relationships and interaction may be no less important [107].

Areas for future research

It is evident from the foregoing that, despite recent interest, geriatric epileptology is a relatively underdeveloped and under-researched field. A number of areas urgently require investigation.

Although it is now clear that cerebrovascular disease is the most common cause of seizures in old age, the relation may be overestimated because of the frequency of vascular disease in the general elderly population. More studies are needed to determine the frequency and types of other causes and, as a corollary, which of these patients are amenable to surgical intervention. Seizure-related fractures and other significant physical injuries are common in elderly patients, and may considerably impact mobility and increase dependence. Similarly, the psychosocial aspects of living with a chronic, stigmatized illness must be studied further. With regard to treatment, many questions remain to be answered. Studies are required to determine whether, and when, one should treat a single unprovoked seizure in old age. The place of newer AEDs such as levetiracetam and pregabalin in the treatment of elderly-onset seizures needs to be assessed prospectively. These studies should focus not simply on the traditional endpoints such as seizure control, but also on the feasibility of reducing subtle adverse effects on, for example, gait and mobility.

Summary and recommendations

Although the goals of treatment are the same in all patients – controlling seizures while minimizing side-effects and their effect on quality of life – there are various issues that make seizure management in elderly patients particularly challenging. These are in large part based upon both physiological changes with age, as well as the high frequency of co-morbid conditions in the elderly. Co-morbidities not only make diagnosis difficult,

but the many co-medications and potential drug interactions can result in suboptimal seizure control and a higher risk of toxicity.

In their approach to the elderly patient with episodic loss of consciousness, clinicians must quickly rule out life-threatening non-seizure diagnoses (usually cardiac causes such as ventricular arrhythmias). Thereafter, the clinician must maintain a high suspicion for seizures, as seizures are not only common in this age group, but frequently present atypically and are mistakenly interpreted as a manifestations of a co-morbid condition (for instance vascular disease). Whenever a diagnosis is in question, video-electroencephalography can help rapidly to confirm or exclude a diagnosis of seizures. The choice of drugs should be based upon adverse effect profile, lack of drug–drug interactions and co-morbid conditions. The newer AEDs should be first-line therapy, assuming no financial barriers. It is also imperative for the clinician to understand age-related pharmacokinetic changes, underlying medical co-morbidities and concomitant medication regimens while starting an AED. It is recommended to start therapy at a low dose and to titrate upwards slowly. In general, we recommend using half the dose and half the titration speed as would be used in a young adult. Finally, close follow-up is essential and compliance is a risk in elderly patients owing to a higher incidence of adverse events, complicated medication regimens and a general lack of social support. Knowledge of an elderly patient's values and expectations is essential in providing high-quality clinical care.

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17 Management of Epilepsy in People with Learning Disabilities

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The same disorder that causes seizures has also, in many patients, the potential to limit intellectual development. Mental retardation is present in more than 20% of adult individuals with epilepsy [1]. The risk of developing a seizure disorder increases with the severity of cognitive deficit. People with learning disabilities represent an important subgroup within the population of patients with epilepsy. Here we are faced with many of the most refractory patients. The general principles in the management of epilepsy are no different than for any other patients [2]; nevertheless, the co-existence of intellectual deficits and behavioural abnormalities can substantially interfere with the medical assessment and treatment of seizures. Adverse drug reactions can remain unrecognized and may be more harmful than the seizures themselves. Particular care should be taken to avoid overmedication in this group. During a lifetime, these patients are among the most drug-exposed groups in society. The treatment objective must not necessarily be a seizure-free state, but improvements in seizure control, alertness, mood and behaviour.

Previously, textbooks often conveyed the impression that the combined occurrence of epilepsy and learning disability is predominantly confined to the younger age groups, but, numerically, adult patients far outnumber children (Fig. 17.1) [3], and comprehensive medical follow-up of this patient category must continue beyond the end of adolescence. This chapter will highlight some particular medical problems and complications which accumulate in patients with learning disabilities and associated handicaps.

Comprehensive epilepsy service

Multidisciplinary approach

The cognitive deficits expressed via intelligent quotient (IQ) level are certainly not the only factor for disability in the large and complex group of patients with learning disabilities. The total social handicap largely depends on concomitant neurological handicaps, such as epilepsy, various motor deficits, sensory impairments and behaviour abnormalities, including autistic features. Many problems are particularly prominent in the paediatric age group, but several continue and some arise in adulthood. Patients with learning disabilities represent a particular challenge to the epileptologist. Investigation and treatment are often hampered by contact problems. These people usually have reduced abilities to express their own wishes and requests. Carers have to be relied upon, and a multidisciplinary and comprehensive approach is often needed. Attention should be focused on several factors other than just the seizures, such as behaviour, alertness, mood, communication, co-operation, appetite and sleep pattern. Comprehensive epilepsy service may be divided into three overlapping fields: the medical, the psychological and the social and educational (Table 17.1). A strong awareness of the need for these different approaches is mandatory for an optimal management of patients with learning disabilities. However, in the global assessment of these patients, care should be taken that the pure medical needs are not overshadowed by other aspects.

Medical aspects

There has been an increasing appreciation of the fact that individuals with learning disabilities are very heterogeneous regarding the pathogenic mechanisms and the clinical manifestations of their brain dysfunction. Because of their special needs, these patients are often excluded from the general epilepsy service, especially in adult practice. EEG recordings may be impossible to perform. The presented history is often inaccurate. The key to a precise evaluation is the detailed observation and description of seizures and behaviour by carers and family members. The fundamental importance of detailed anamnestic data, including those from good informants, must be emphasized. The seizure semiology may be atypical. Seizure clustering and transitions between various seizure types are common. In patients with limited understanding and verbal ability, the attacks may be coloured by emotional responses and behavioural reactions. Non-epileptic, seizure-like behaviour is common. A range of paroxysmal events other than epileptic seizures may occur in these patients (Table 17.2) and misinterpretations by caregivers are common. To improve diagnostic accuracy, home video recordings may be helpful. These patients may be more prone to inadequate, long-term antiepileptic drug (AED) treatment than other patients. Inappropriate epilepsy treatment often starts with an insufficient history, particularly in adult patients who are accompanied by caregivers with a limited knowledge of their clients. Information about the individual's past and current health status is the basis of clinical decision-making. Optimal medical management of these patients is often very time-consuming. A specialist epilepsy nurse may play a key role in the service to them, providing supervision of the carers and warranting availability and continuity of high-quality medical care.

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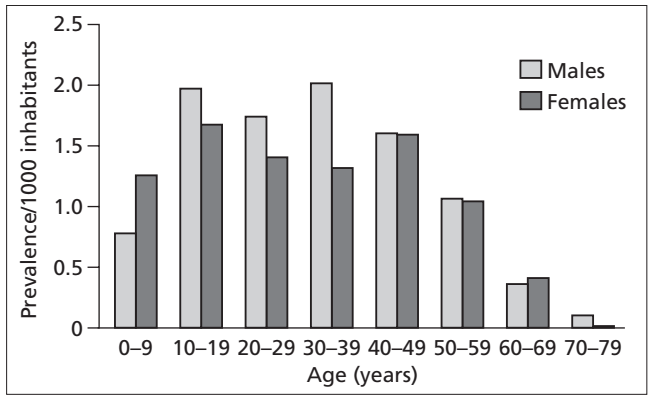

Fig. 17.1 Prevalence rates by age and sex of 299 persons with epilepsy and learning disability in the county of Västerbotten, Sweden. Redrawn from ref. 3 with permission from Elsevier Science.

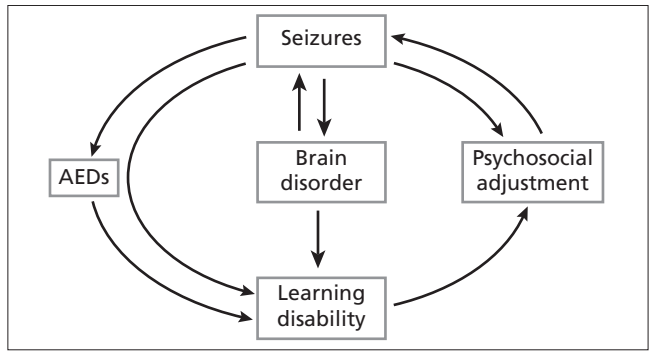

Fig. 17.2 In people with learning disability, overtreatment with antiepileptic drugs may enhance cognitive dysfunction, impair psychosocial adjustment and increase behavioural problems. The various factors may be difficult to identify and may interact in different ways in different patients. Redrawn with permission from Wrightson Biomedical Publishing.

Table 17.1 The three overlapping fields of comprehensive epilepsy service to people with learning disabilities.

Medical	The need for continuous access to current developments in diagnosis and treatment throughout all age groups
Psychological	The need to consider the symptoms and the treatment in relation to psychological and intellectual functioning
Social	The need for social and educational support, and for information and supervision not only for the sufferer, but also for the family and the carers

Table 17.2 Paroxysmal non-epileptic events in patients with learning disability.

Spasms and dyskinesias in co-morbid cerebral palsy
Stereotypes and self-stimulation in patients with autistic features
Activity pauses
Acute dystonia and tardive dyskinesias in patients receiving psychopharmacological treatment
Episodic dyscontrol and attention seeking in patients with behavioural problems
Gastro-oesphageal reflux

Psychological and cognitive aspects

Seizure effects and adverse AED reactions may be masked by the intellectual handicaps. Drowsiness, mood change and behavioural problems may be signs of drug toxicity. Side-effects, neurodeficits, seizure activity and social, educational and behavioural problems often merge. The various factors are sometimes difficult to identify and they may interact in different ways in different patients (Fig. 17.2). In particular, it is important to distinguish between permanent learning disability on the one hand and state-dependent learning disability (pseudo-retardation) on the other [4]. Both forms often occur together. State-dependent learning disability is reversible and potentially treatable, but unfortunately often goes unrecognized. In patients with epilepsy, it may be of two kinds: either drug induced or seizure related, due to epileptiform discharges, subtle or 'subclinical' seizures or postictal effects. When treating patients with learning disabilities, it is imperative to bear in mind the complex inter-relationship between cognitive function and epilepsy-related factors (Fig. 17.2).

Social and educational aspects

Myths and prejudices still persist about patients with learning disability which should be countered by all members of the care team. There is often a long-term and continuing need for social and educational support, not only for the sufferer but also for the family and other persons in the patient's environment. The transfer of competence to the community caregivers should be given high priority. Specialist epilepsy nurses should be assigned the responsibility for providing counselling and relevant information under the supervision of an epileptologist, and for ensuring that each patient has the possibility of taking full advantage of all available services. Close co-operation and co-ordination between the various professions at all levels of health care are essential parts of a well-organized comprehensive treatment programme. The quality of these services should be equally distributed without regard to age, intellectual level or geography. Meaningful occupation and activities improve well-being, enhance psychosocial adjustment and contribute to improved seizure control. Epilepsy management needs to be integrated into the larger context of comprehensive quality care, in which services to the mentally retarded and patients with acquired cognitive deficits form an essential part.

Antiepileptic drug treatment

Compliance

A prerequisite for the successful therapy of epilepsy is good drug compliance that ensures a stable medication effect. People with intellectual disability do not always accept taking tablets, especially large tablets. In multiply handicapped individuals, additional impairments in the form of swallowing problems and/or behavioural abnormalities may interfere with the oral intake of solid formulations. Drugs that are available as liquid, soluble, powder or granular formulations for children may be useful in the mentally retarded adult (Table 17.3). To maintain adequate prophylactic treatment, the rectal route may sometimes be necessary. Suppositories of carbamazepine and valproate are available. When intravenous administration is impossible or inconvenient, the liquid peroral form may, in exceptional situations, be given

Table 17.3 Measures supporting drug compliance in handicapped patients with swallowing difficulties or co-operation problems.

Severe multiple handicaps	Mild cognitive deficits
Alternative drug formulations: *Liquid* (carbamazepine, valproate, levetiracetam); *Soluble tablets* (carbamazepine, lamotrigine); *Powder* (vigabatrin); *Sprinkle* (topiramate, valproate)	Drug dispenser Alarm wristwatch Simple dosing tailored to individual habits and daily routines Social support with regular nurse visits

Table 17.4 Adverse reactions of traditional AEDs causing particular concern in patients with learning disabilities.

Phenobarbital	Somnolence, mood disturbances, behaviour disorders, including hyperactivity
Phenytoin	Cognitive impairment and cerebellar symptoms (phenytoin encephalopathy) after long-term use Gingival hyperplasia, particularly in patients with poor oral hygiene
Carbamazepine	Seizure aggravation in symptomatic generalized epilepsies
Valproate	Severe hepatotoxicity, particularly in mitochondrial disorders Tremor Weight gain

rectally. Patients with severe nutritional problems who require tube feeding and percutaneous gastrostomy also need drugs in fluid or soluble forms. The caregivers are extremely important partners in the treatment of this patient category. The need for education and guidance concerning the goals of therapy and the importance of adherence to the prescribed regimen is obvious.

Patients with only mild intellectual deficits who live partly independently but have an irregular behaviour may need various other measures to enhance drug compliance, including drug dispensers, alarm wristwatches and a social support system which may include regular nurse visits at medication times. Dosing should be kept as simple as possible and the drug intake tailored to their individual habits and activity programmes (Table 17.3). In training for autonomy and independent living, self-medication should not be given early priority. When memory is reduced and the understanding of the need for prophylactic medication inadequate, close supervision is necessary to maintain sufficient treatment. Non-compliance is a significant problem in intractable epilepsy, and may be prevalent particularly in people who have an impaired ability to comprehend information or express views and discuss feelings about the drugs and their effects.

Old drugs

The traditional medications, including phenobarbital, phenytoin, carbamazepine and valproate, are all effective in controlling seizures, but their utility is hampered by their adverse effect profiles and unwanted drug interactions. In patients with intellectual disabilities, some specific issues concerning these drugs need to be taken into account (Table 17.4).

Phenobarbital

Phenobarbital is not considered a first-line agent due to its association with somnolence, irritability and mood disturbances. The most consistent problems in patients with learning disability are the tendencies to exacerbate behaviour disorders, cause hyperactivity, and also to cause sleepiness and depression [5].

Phenytoin

Phenytoin is also not recommended as a first-choice drug due to its potential adverse effects. Patients with severe brain damage who are receiving multiple AEDs are particularly susceptible to the toxic effects of phenytoin, even at low plasma concentrations. Phenytoin encephalopathy is a rare complication, manifested as cognitive impairment and cerebellar symptoms, which may be partly related to the dose-dependent kinetics of the drug, individual differences in drug metabolism and polytherapy. The long-term use of phenytoin is not recommended for patients with loss of locomotion, marked cognitive impairment, or symptoms and signs of cerebellar disease. Phenytoin encephalopathy can progress if exposure to the drug continues. In progressive myoclonic epilepsy of Baltic type, phenytoin has been said to accelerate the disease process, an effect which, in part, has been reversible after switching to valproate [6].

Carbamazepine

Carbamazepine remains one of the most commonly prescribed drugs for partial epilepsy. It is also indicated in the treatment of neuralgias and manic–depressive disorders. Because of its minimal unwanted effects on cognition and behaviour, carbamazepine is an excellent drug for the treatment of people with learning disability and epilepsy. Nevertheless, one should bear in mind that patients with cognitive impairment may have a particularly low threshold for neurotoxicity and that carbamazepine may sometimes have a seizure-inducing effect in these patients, especially in those with symptomatic generalized epilepsies [7].

Valproate

Valproate is a first-line drug in the treatment of primary generalized seizures, but also has effect in other seizure types. It remains the backbone in the treatment of Lennox–Gastaut syndrome because it is effective against multiple seizure types [8]. Particularly in the area of intellectual disability, severe liver toxicity is an important but rare idiosyncratic adverse reaction. Developmental delay and inborn errors of metabolism, particularly mitochondrial disorders, represent risk factors for valproate hepatotoxicity. Particular care should be taken with this drug when such conditions can be suspected, and it should be avoided when a known mitochondrial dysfunction is present. Other predisposing factors are young age, polytherapy and stressful conditions, such as infections and underlying liver disease [9].

New drugs

The newer AEDs broaden the therapeutic options in patients with refractory epilepsy. Several of these drugs have obtained a particular place in the treatment of patients with learning disabilities [10–12]. All of them may have strengths as well as drawbacks in this large and heterogeneous patient group (Table 17.5). Most studies on the treatment of these patients are postmarketing

Table 17.5 Strengths and drawbacks of commonly used new AEDs in treatment of patients with learning disabilities.

Drug	Strengths	Drawbacks
Vigabatrin	Effective in infantile spasms	Visual field defects Psychiatric side-effects Weight gain
Lamotrigine	Broad spectrum Effective in Lennox–Gastaut syndrome Non-sedating Increased attention and alertness	Behaviour problems in some Sometimes exacerbation of myoclonia Skin rashes
Felbamate	Broad spectrum Effective in Lennox–Gastaut syndrome Non-sedating Increased alertness	Bone marrow and liver toxicity Regular laboratory monitoring Insomnia Behaviour problems Anorexia, weight loss
Topiramate	Broad spectrum Effective in Lennox–Gastaut syndrome	Potential cognitive side-effects Anorexia, weight loss
Gabapentin	Effect in pain and anxiety Psychotropic effects	Narrow spectrum (partial epilepsy) Behaviour problems in some Weight gain
Oxcarbazepine	Less interactions and improved tolerability compared with carbamazepine	Hyponatraemia Potential seizure aggravation in symptomatic generalized epilepsies
Tiagabine	Antispastic effect?	Narrow spectrum (partial epilepsy) Dizziness, asthenia, tremor, depression
Levetiracetam	Broad spectrum	Behaviour problems in some Irritability, aggression
Zonisamide	Broad spectrum	Central nervous system side-effects
Pregabalin	Effect in pain and anxiety	Narrow spectrum (partial epilepsy) Weight gain Limited experience
Rufinamide	Efficacy in Lennox–Gastaut syndrome	Limited experience

surveillances, but two epilepsy syndromes which are strongly associated with learning disabilities have recently been the subject of several drug trials: infantile spasms (Chapter 13) and Lennox–Gastaut syndrome (Chapter 14). In Lennox–Gastaut syndrome, double-blind controlled studies have demonstrated efficacy for felbamate, lamotrigine, topiramate and rufinamide [8,13].

Vigabatrin

Vigabatrin has a specific role in the treatment of infantile spasms, particularly when due to tuberous sclerosis. However, the risk of constricted visual fields is difficult to assess in this group [14,15]. Perimetric follow-up is recommended, but standard visual field examinations require a mental level corresponding to at least 9 years. Psychiatric (depression, psychosis) and behavioural side-effects can also be difficult to identify in patients with learning disabilities.

Lamotrigine

Lamotrigine is effective in partial seizures and a wide range of generalized seizures. Tolerability is usually excellent. Synergistic effect with valproate has been reported [16]. Lamotrigine has shown efficacy in patients with symptomatic generalized epilepsies, including Lennox–Gastaut syndrome [8]. It has mood-stabilizing effects, and benefits on behaviour have been demonstrated in patients with learning disabilities. It is usually not sedative and may increase attention and alertness, particularly in children with developmental problems. Improved social engagement has been reported [17,18]. On the other hand, aggravated hyperactivity and irritability have occasionally also been attributed to lamotrigine [19]. The exacerbation of myoclonic seizures has been noted, as well as the emergence of various dyskinesias including blepharospasm, tics and Tourette-like symptoms, particularly in patients with pre-existing central nervous system (CNS) dysfunction [20].

Felbamate

Felbamate is a potent drug with efficacy across a range of seizure types. It has a documented beneficial effect in Lennox–Gastaut syndrome, particularly in atonic seizures, but the use of felbamate is restricted due to potential toxicity in the bone marrow and liver. Blood tests are recommended at least every 2 weeks during the first 3 months of treatment, a practice which may be continued for 6–12 months [21]. This can be difficult to perform in some patients with learning disabilities. Education of caregivers regarding early clinical symptoms and signs of aplastic anaemia and liver failure is important. Insomnia, anorexia and weight loss are common side-effects. Of particular concern is the effect of felbamate on behaviour in the developmentally delayed population. Anxiety and irritability have been noted [18]. However, as with other non-sedating AEDs, brightening and improvement of alertness may also occur, an effect which may be related to improved seizure control. Pharmacokinetic interactions complicate its use in combination therapy. Nevertheless, felbamate has a risk–benefit ratio that allows its use in selected patients with refractory epilepsy [21].

Topiramate

Topiramate is a potent broad-spectrum drug which is also effective in primary generalized seizures. It has documented effect in Lennox–Gastaut syndrome and may be of benefit in myoclonic seizures [8]. Surprisingly, in one double-blind placebo-controlled study in a broad category of patients with learning disability and uncontrolled seizures, efficacy was not confirmed, probably due to insufficient dosing, underpowered design and problems with exact seizure recording [22]. Treatment has been associated with cognitive complaints such as mental slowing, mostly in the form of reduced verbal fluency and particularly when the drug is used in polytherapy. A subgroup of patients seem to experience a reversible worsening of pre-existing neurodeficits, such as speech difficulties and even hemiparesis. Behavioural disturbances can also occur. Nevertheless, many patients with learning disabilities tolerate the drug well [22,23] and it has also been reported to reduce aggression and agitation in some with developmental disability [12].

Gabapentin
Gabapentin is indicated for partial and secondary generalized seizures. It has a favourable side-effect profile and may reduce anxiety and also give relief of painful spasms in patients with cerebral spasticity. The drug has been shown to improve rating scales on a range of behavioural parameters, including co-operation, restlessness and challenging behaviour [17]. However, adverse reactions in the form of aggression, hyperexcitability and tantrums have also been reported. This is more common in patients with pre-existing behavioural difficulties and developmental delay. Even rare cases of involuntary choreiform movements and myoclonus have been reported in neurologically impaired patients [24], an unusual reaction that gabapentin shares with several other AEDs, such as phenytoin and lamotrigine. Unfortunately, gabapentin often has very limited antiepileptic efficacy in the severe therapy-resistant epilepsies of learning-disabled patients [25,26].

Oxcarbazepine
Oxcarbazepine is similar to carbamazepine in its mechanism of action. It exerts its antiepileptic effect through its monohydroxy derivative and is not metabolized into an epoxide. Compared with carbamazepine, it has fewer pharmacokinetic interactions and improved tolerability. It can, however, aggravate or induce generalized seizure types and worsen EEG features in some patients [27]. It can also reduce impulsive aggression [12]. Hyponatraemia may be more common than with carbamazepine, an effect which may be particularly pronounced in patients with central nervous dysfunction with altered fluid intake patterns and central nervous dysregulation of water balance.

Tiagabine
Tiagabine is also effective in partial seizures and has little impact on cognition. Dizziness, asthenia, tremor and depression are amongst its side-effects. In contrast to vigabatrin, which increases γ-aminobutyric acid (GABA) by inhibiting GABA transaminase intracellularly, tiagabine increases GABA in the synaptic cleft by reuptake inhibition. This compartment difference probably explains why tiagabine does not seem to share the serious retinotoxic effects with vigabatrin [15]. There is little experience with this drug in the learning-disabled population [26]. In spite of a mechanism of action similar to vigabatrin, tiagabine has not been trialled in West syndrome.

Levetiracetam
Levetiracetam is a broad-spectrum AED. It generally causes few side-effects and may be a good option in patients with encephalopathies and multiple seizure types. A beneficial effect has been reported in patients with progressive myoclonic epilepsy [28]. However, in a minority of patients severe behavioural side-effects do occur, usually in the form of irritability and aggression. This is a particular problem in people with learning disability [29] and in patients with a previous history of aggression [30]. This effect seems in part to be dose related. In other patients, alertness and behaviour may improve.

Zonisamide
Zonisamide is also effective in partial as well as in generalized seizure types, but has a potential for problematic side-effects. Of particular interest are the reports of efficacy against myoclonic seizures, and it has been reported to be of specific benefit in progressive myoclonic epilepsies [31].

Pregabalin
Pregabalin has a similar narrow-spectrum antiepileptic profile to gabapentin, but is considered a more potent drug. Evidence-based efficacy is also demonstrated in various anxiety and pain disorders [32]. Experience in the learning-disabled population is as yet quite limited.

Rufinamide
Rufinamide modulates the activity of sodium channels. Efficacy in partial seizures and in Lennox–Gastaut syndrome has been demonstrated. In Lennox–Gastaut syndrome, tonic and atonic seizures appear to respond particularly well [13]. However, in patients with multiple seizure types, the frequency of one seizure type can sometimes decrease while another increases.

Further prospective studies comparing efficacy and tolerability, including rating scales on behaviour parameters and other measures adapted for people with intellectual deficits, should be performed to collect more systematic clinical experience in these patients [2,22]. However, trial methodology is difficult due to the heterogeneity of aetiologies and of underlying mechanisms, various co-morbidities, as well as the frequently limited number of patients within one specific subgroup. There are also complex and difficult ethical issues.

Mechanistic considerations

The neurobiology of specific disorders can influence drug choice in certain situations. Several of the adverse reactions of valproate are caused by its effects on mitochondrial function and other enzymes. Valproate inhibits mitochondrial oxidation and facilitates the formation of hepatotoxic metabolites [9]. Hence, this drug should be avoided in mitochondrial disorders. Valproate can also have a negative impact on the underlying biochemical disturbance of Rett's syndrome. This phenomenon may be related to the inhibition of histone deacetylase, which increases the effect of a defective methyl-CpG-binding protein 2 (MeCP2) on the hyperacetylation of histones. Sodium channel blockers may be a better choice in many patients with Rett's syndrome [33]. In contrast, in Angelman's syndrome, carbamazepine and oxcarbazepine are typically not effective and may result in worsening of seizures. In this disorder, the pathophysiological mechanism involves a defect in the DNA coding for subunits of the $GABA_A$ receptor. Accordingly, drugs with GABAergic mechanisms, such as valproate and clonazepam, as well as topiramate, have been reported to be effective [11]. A paradoxical effect of vigabatrin in generalized epilepsies may be caused by an excessive stimulation of $GABA_B$ receptors by a diffuse increase of GABA in the brain. Nevertheless, vigabatrin is now the treatment of choice for infantile spasms in tuberous sclerosis and cortical dysplasia. A reduction in GABAergic interneurone density and a decreased release of GABA have been demonstrated within the cytoarchitectural abnormalities of developmental lesions [14]. The identification of mutations in the sodium channel α_1-subunit (SCNA1) in patients with severe myoclonic epilepsy of infancy and other early-onset epileptic encephalopathies has been an important

advance in the understanding of these disorders [34]. It is to be hoped that we will soon be able to specifically target these genetic defects therapeutically and that future translational research will be able to uncover other pathophysiological mechanisms which lead to more targeted and rational treatments of both the epilepsy syndromes and the neurocognitive deficits.

Central nervous system side-effects

In people with learning disability, it can often be difficult to achieve a satisfactory balance between seizure control and adverse drug effects. These patients may not be able to report the early symptoms of toxicity, such as sedation, blurred vision and ataxia. Subtle cognitive adverse reactions may occur unnoticed by the carers. Side-effects may also sometimes manifest themselves indirectly as behavioural problems [18,35] (Fig. 17.2). Sedation may manifest as hyperactivity. Stress and restlessness may be converted from somatic side-effects (e.g. diplopia).

The four traditional front-line AEDs – phenobarbital, phenytoin, carbamazepine and valproate – have all been reported to be associated with dose-related cognitive side-effects, foremost in the form of slowing of central information processing. These may be considerable for phenobarbital and possibly larger for phenytoin than for carbamazepine and valproate. A chronic phenytoin encephalopathy may occur, particularly in patients with pre-existing neurodeficits, even with plasma levels within the acceptable range [6]. Some of the new drugs are claimed to have favourable cognitive profiles [35], but reliable data are sparse. As mentioned, topiramate can cause cognitive impairment, but this can often be avoided by gradual initial titration. Some pharmacodynamic interactions may be of particular relevance in this patient group. The combination of lamotrigine and carbamazepine can enhance central nervous side-effects. A person unable to express these problems verbally may instead react with disturbed behaviour [18]. Valproate-induced tremor may be aggravated by lamotrigine, particularly in neurologically impaired individuals.

Clinical experience suggests that patients with learning disabilities are often more vulnerable to cognitive side-effects than other patients. However, the subgroup of patients with severe intellectual handicaps is excluded from the ordinary 'pencil and paper' tests of cognitive functions and mood. In lesional epilepsy, specific cognitive abilities are affected (depending on the site of the lesion, e.g. language functions). In monotherapy with carbamazepine and valproate, a subgroup of patients with brain lesions and pre-existing cognitive deficits shaved a significant decrease in memory performance during medication [36]. The existence and extent of underlying brain damage both seem to influence the adverse cognitive effects of a particular drug. Furthermore, mood effects can occur with some AEDs, particularly with barbiturates, vigabatrin and topiramate [37], which indirectly affect cognitive performance.

Many patients with learning disabilities have an inappropriate and excessive medication load that impairs their quality of life. Reduction of undue polytherapy should always be aimed at [38]. A pitfall in the evaluation of more effective and better tolerated treatments in the severely retarded patient lies in the fact that increased alertness and self-assertion may be misinterpreted as behavioural side-effects, the so-called release phenomenon [18]. A more demanding behaviour should not be invariably considered as a sign of toxicity. Such symptoms should be analysed carefully before a new treatment is abandoned. Environmental support and activity programme adjustments may be needed to meet new requirements of more attentive patients. It has been emphasized repeatedly that AED therapy should not exclusively focus on seizure freedom. Patients who, for reasons other than their epilepsy, cannot achieve independent living may tolerate incomplete seizure control better than others.

Table 17.6 Factors predisposing to paradoxical AED-induced aggravation of seizures.

Young age
Multiple seizure types
Prominent epileptiform EEG activity
Learning disabilities and behavioural disorders
Polytherapy
Drug-induced drowsiness

Paradoxical effects

Some AEDs occasionally aggravate epilepsy, and cause increased frequency and severity of seizures. This can be mediated by the non-specific effects of sedation and overtreatment, or can occur as a more specific effect in some seizure types or epilepsy syndromes [7]. Factors predisposing to such effects are listed in Table 17.6. More frequent seizures may be a part of the clinical picture of the insidious phenytoin encephalopathy [6]. There is evidence that carbamazepine and oxcarbazepine may aggravate seizures, particularly 'minor' generalized seizures, and in some patients even generalized tonic–clonic seizures [27]. In symptomatic generalized epilepsies, several seizure types that respond differently to treatment may co-exist. In the Lennox–Gastaut syndrome, carbamazepine may be effective for tonic seizures, but can aggravate atypical absences and myoclonic or atonic seizures. Benzodiazepines can cause an increase in tonic seizures in the same disorder. Vigabatrin and other GABAergic drugs can aggravate generalized seizures (particularly absence, tonic and myoclonic seizures, and even generalized tonic–clonic seizures). Lamotrigine, as well as levetiracetam, can also increase seizure frequency. Lamotrigine has a negative effect in severe myoclonic epilepsy of infancy [7]. In one report, a paradoxical effect of levetiracetam, including the emergence of *de novo* generalized tonic–clonic seizures, appeared most often in patients with learning disabilities [39]. Tiagabine may precipitate non-convulsive status. The clinician should not forget that seizure aggravation may occur as part of the rare valproate hepatotoxicity, which may occur particularly in young children with metabolic disorders [9]. Increased seizure frequency can also occur within the context of a toxic valproate encephalopathy, not necessarily associated with high drug plasma levels, often accompanied by confusion, lethargy, ataxia and hyperammonaemia. Drug-induced drowsiness and inactivity alone may probably contribute to seizure induction in some multiply handicapped patients. Not surprisingly, in patients receiving excessive polytherapy, an improved seizure control may occur when their drug load is reduced [38].

Paradoxical drug reactions are probably widely underestimated in patients with intractable epilepsy, particularly in patients with

intellectual deficits who cannot themselves express their opinions about the prescribed treatment. It is often overlooked by the non-specialist, and even by the carers, as the history is often insufficient due to a lack in the continuity of information sharing. Appropriate follow-up is imperative when prescribing new drugs to these patients.

Can the disease process be influenced?

There is little scientific evidence to suggest that AEDs improve the prognosis of the underlying disorders, beyond their ability to control seizures. However, in some epileptic encephalopathies in childhood, the antiseizure effects appear to be of paramount importance for cognitive development. The so-called catastrophic epilepsies of childhood have their onset in patients younger than 5–6 years of age [31] during the critical period for brain maturation and developmental plasticity. Frequent seizures and/or abundant epileptiform activity may disrupt pathways necessary for cognitive maturation, leading to long-term cognitive deficits [40]. Harmful neuronal reorganization in the form of abnormal synaptic connections may be generated. In these epilepsies of childhood, it has been suggested that controlling seizures does alter the outcome of intellectual functioning. In patients with a history of infantile spasms, the patients who quickly become spasm free are those who are developmentally normal. In children with tuberous sclerosis, the occurrence of autistic regression is often clearly linked to the onset and presence of seizures [41]. Follow-up indicates that controlling secondary generalization induced by infantile spasms represents a key factor for mental and behavioural development. Hence, prompt and effective prophylactic antiepileptic treatment is crucial for these patients.

In prolonged and serial seizures, early and successful acute treatment can improve outcome. After severe status epilepticus, persistent neurocognitive impairment varies with the type and aetiology of epilepsy, the severity of the status, and the age of the patient. In severe and complicated febrile seizures, excitotoxic cell death in the hippocampus may be responsible for the progression of future uncontrolled spontaneous seizures and sometimes for permanent neurological deficits, as in the hemiconvulsion hemiplegia epilepsy (HHE) syndrome [42].

Non-pharmacological treatment

Epilepsy surgery

Patients with learning disabilities can benefit from epilepsy surgery, and cognitive deficits should not be considered a contraindication to resective epilepsy surgery. However, there is a lower probability of a good seizure outcome in patients with low IQs because of the association with diffuse or widespread brain damage. This was shown in a recent national survey from Sweden, where IQ level was an independent predictor of seizure freedom. Nevertheless, many of the low-IQ patients did have a beneficial effect of surgery, especially those with lesions [43]. Patients with neurodeficits and uncontrolled mesial temporal lobe seizures due to the HHE syndrome are good candidates for surgical treatment [42]. Studies have generally not supported the fear that further deterioration of cognitive function and social adjustment will occur after resective treatment [44]. On the contrary, seizure control from surgery at an early age can lead to a catch-up development [45]. Disconnective surgery, such as corpus callosotomy, can occasionally be beneficial in symptomatic and cryptogenic generalized seizures, for instance in Lennox–Gastaut syndrome (Chapter 74), where the operation can reduce the number of generalized tonic–clonic seizures by preventing their generalization from partial onset, and also lower the number of drop attacks, including atonic seizures [46]. Other options include hemispherectomy and multiple subpial transections (Chapters 73 and 75).

Vagus nerve stimulation

Vagus nerve stimulation (Chapter 81) is said to benefit patients with refractory partial epilepsy and learning disabilities. Promising results have been reported in children and adults with symptomatic generalized epilepsy, including Lennox–Gastaut syndrome [46]. Open studies purport to show improved seizure frequency and severity and to reduce clustering and the duration of the postictal period. Unfortunately, the antiepileptic effect is modest in most patients. Nevertheless, this method is free from cognitive adverse effects and may reduce the drug burden. Vagus nerve stimulation has been reported to improve alertness, mood and verbal ability in this category of patients [47] and also has a potential as an antidepressant therapy. In some patients with cognitive deficits, the full compliance ensured by the automatic delivery of this form of therapy can be a particular advantage. On the other hand, severely multi-handicapped individuals might be at an increased risk for certain rare complications, such as vagus-mediated worsening of motor bulbar impairments and aspiration pneumonia.

Ketogenic diet

The enthusiasm for this therapeutic option has fluctuated over the last 50 years. The diet is high in fat and low in carbohydrate and protein and has been employed mainly in children with significant neurological handicaps, particularly in Lennox–Gastaut syndrome. The diet can be very unpalatable. It requires strict supervision and has serious limitations and potential adverse effects. In patients with cognitive or behavioural problems implementation may be difficult. A modified Atkins diet might be better tolerated. The diet is discussed in more detail in Chapter 23.

Acute seizure treatment with benzodiazepines

Clusters of seizures, prolonged seizures and status epilepticus are common complications in the developmentally delayed population. Impending status epilepticus needs swift and effective action. The rectal administration of diazepam has long been widely employed in the emergency treatment of all kinds of epileptic seizures. It is given by parents, teachers and care staff without medical or nursing training. This route may provide therapeutic levels within a few minutes.

The rectal administration of diazepam has definitely resulted in a safer existence to many patients with refractory epilepsy and learning disabilities. However, in individuals with poor seizure control, problems from excessive and too-frequent administration can occur, particularly when the carers are insecure and insufficiently trained. Tolerance and dependence may develop during long-term treatment. Withdrawal symptoms,

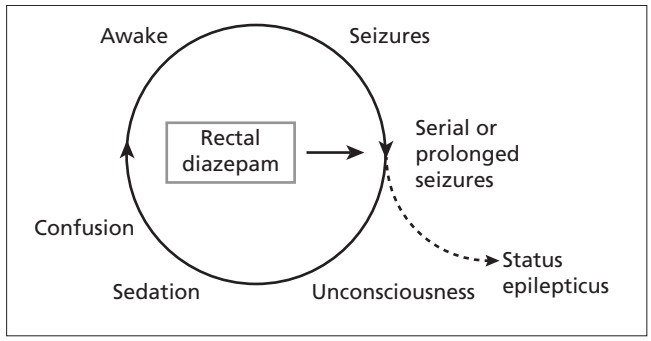

Fig. 17.3 The vicious circle of excessive rectal diazepam treatment in refractory epilepsy. A pattern of cyclic reappearance of prolonged seizures every 3–5 days, interrupted by diazepam and followed by sedation and gradual awakening may be characteristic for this complication. Redrawn with permission from Wrightson Biomedical Publishing.

including seizures, occur if the treatment is stopped after regular administration. Intermittent, large and frequent rectal diazepam doses administered at will cause fluctuations in the plasma drug levels which in themselves can be seizure inducing. Toxic effects, withdrawal and seizure activity can be difficult to manage. Some patients, after long-term use of rectal diazepam, enter a vicious circle, which cannot be broken before the use of the drug is restricted. A cyclic reappearance of prolonged seizures every 3–5 days, interrupted by diazepam, and followed by sedation and gradual awakening, is a characteristic pattern [48] (Fig. 17.3). Non-convulsive status epilepticus may sometimes occur. When restricting intermittent diazepam intake, seizures, wakefulness and behavioural problems can improve. If this strategy proves difficult, oral benzodiazepines in low doses is another option.

Adequate counselling and medically appropriate written directions for the rectal administration of diazepam are mandatory both for patient security and for the legal position of caregivers. The correct and successful use of rectal diazepam depends to a great extent on the competence of the caregiver. The frequency of rectal administration of diazepam should not approach twice weekly for prolonged periods, and it should not be routinely used in short, non-life-threatening seizures lasting less than 2–4 min.

Buccal (or nasal) delivery of midazolam may now be a more convenient and socially acceptable acute treatment of seizures (see Chapters 18 and 34). As with rectal administration, this route also has the advantage of bypassing the portal circulation to avoid first-pass hepatic inactivation.

Concomitant psychopharmacological treatment

Maladaptive, violent or self-injurious behaviour is not unusual in individuals with severe intellectual disabilities. Autistic behaviour is particularly common in children with developmental delay and epilepsy. An exact psychiatric diagnosis is usually difficult to obtain in the severely retarded, but patients with severe learning disabilities or brain lesions often need concomitant antiepileptic and antipsychotic treatment. A range of pharmacodynamic or pharmacokinetic interactions can occur [49]. High doses of antipsychotic drugs can provoke seizures, particularly in patients with organic brain dysfunction [50]. AEDs can induce or aggravate behavioural problems [18,35], which may lead to the prescription of antipsychotic drugs. These drugs can also have cognitive side-effects that compound the effects of the AED. Conversely, enzyme-inducing AEDs, such as carbamazepine, phenytoin and phenobarbital, can profoundly lower the plasma levels of antipsychotic drugs.

Table 17.7 Seizure-inducing properties of some antipsychotic drugs.

High	Clozapine Chlorpromazine
Moderate	Perphenazine and olanzapine Quetiapine Risperidone
Low	Haloperidol

Clozapine and chlorpromazine are among the most proconvulsant antipsychotics. The tendency to provoke seizures is less pronounced with agents that have prominent extrapyramidal side-effects. The seizure-aggravating effects of most atypical antipsychotics are usually modest. Risperidone and quetiapine appear to be less likely to have proconvulsant effects than olanzapine. However, there is, as yet, limited experience with many of these newer drugs in patients with epilepsy. The ranking of the tendencies to precipitate seizures of these drugs in Table 17.7 is not based on accurate data, as doses, co-medication and risk factors for seizures vary among patients. Tricyclic antidepressants may also induce seizures, whereas serotonin reuptake inhibitors have been reported to have antiepileptic effects in open-label studies [49,51]. Polypharmacy with various drugs having the potential to influence the seizure threshold is common in patients with learning disabilities or encephalopathies.

The cause of acute seizure exacerbation in the presence of psychiatric co-morbidity is often complex. Drug toxicity is only one of several subthreshold factors among a cascade of other events, including emotional factors, lack of sleep, stress and possibly the psychiatric disorder in itself. Concomitant withdrawal from benzodiazepines and initiation of antipsychotics carries a risk of seizure breakthrough. A detailed account of all current and recently discontinued medications, even as-needed prescriptions, is of major importance in the evaluation of seizure exacerbation in this population.

The seizure-inducing properties of antipsychotic drugs at small to standard doses should not be overestimated. In some patients, low doses may probably improve seizure control, possibly by suppressing emotional seizure-inducing factors. However, high doses, or an abrupt large dose increase, should be used with caution, especially with antipsychotic drugs with a high potential to lower the seizure threshold [50]. When treating patients with psychiatric co-morbidity, it is essential to be aware of the fact that AEDs themselves possess psychotropic properties, negative as well as positive (Tables 17.4 and 17.5). Atypical behavioural responses are more likely to occur in children and individuals with cognitive deficits. Several AEDs have a role in the treatment of psychiatric conditions [49], including

agitation and aggression in patients with dementia and learning disability [12].

Prognosis of epilepsy in learning disabled patients

Overall prognosis

In about 25% of patients with newly diagnosed epilepsy, seizure control is not possible with the present AEDs. However, in studies of prevalence of epilepsy, the proportion of uncontrolled epilepsy is larger. In a large Swedish study, 57% of patients had experienced seizures during the previous year, and the mean yearly seizure frequency was higher in subjects with mental retardation than in others [1]. Severe epilepsy is significantly related to early onset [52]. In prospective studies, associated neurological or cognitive handicaps have consistently been reported to have an adverse effect on the outcome of epilepsy. Malformations of cortical development are often associated with refractory seizures. These conditions range from the extreme example of lissencephaly, with a smooth cortex and severely affected brain function, to less distinct syndromes with nodular heterotopias and localized cortical dysgenesis with mild clinical symptomatology. In studies correlating aetiology and treatment response in partial epilepsy, cortical dysgenesis had the second worst prognosis after mesial temporal sclerosis [53]. In the catastrophic epilepsies of childhood, the long-term prognosis is generally very poor. A high seizure activity is associated with developmental stagnation or regression in these conditions [4,31].

Nevertheless, the spectrum of seizure disorders in individuals with learning disability is wide, ranging from the most severe and intractable epilepsies to disorders with only isolated attacks, an important fact to bear in mind [11,16,52]. Some patients with severe intellectual deficits may develop generalized tonic–clonic seizures in adult life, even in the absence of prior epilepsy or a diagnosis of Down syndrome. When late-onset epilepsy occurs in such patients without the presence of overt recent or current brain damage, the outlook is usually good [52].

Specific diagnoses are relevant for the prognosis of seizure disorders, even in adulthood. Some examples are detailed below.

Down syndrome

With advancing age, an increased incidence of epilepsy has been demonstrated in Down syndrome, in one study reaching 46% in those over 50 years [54]. Late-onset myoclonic epilepsy in Down syndrome is associated with massive myoclonic jerks, tonic–clonic seizures and progressive dementia [55]. The generalized tonic–clonic seizures seem to respond well to AED treatment in the early stages, but the tendency to seizures usually progresses. The myoclonus may be intractable. AEDs often cause marked side-effects even at plasma levels well within the 'therapeutic' range.

Rett's syndrome

Most girls (80–90%) with Rett's syndrome have epilepsy starting somewhere between 3 and 5 years. The seizures are of various types; many are partial. The seizure frequency appears to peak in the age group of 7–12 years. In adulthood, the epilepsy often improves considerably and can occasionally remit [56]. Many of these profoundly retarded females tend to react adversely to standard antiepileptic regimens, particularly to valproate [33]. Withdrawal of AEDs should always be considered in seizure-free women with Rett's syndrome.

Angelman's syndrome

Epileptic seizures occur in over 90% of patients with Angelman's syndrome, often with onset before 3 years of age. Multiple seizure types can be seen, generalized tonic–clonic seizures, atypical absences, myoclonic seizures and tonic seizures. Epilepsy predominates in childhood, but can persist or reappear in adulthood. The prognosis may be related to the type of 15q11–q13 abnormality. Sustained seizure freedom has been found in four of five patients with deletions [57].

Fragile X syndrome

Epilepsy is present in about 20% of mentally retarded patients with this chromosomal abnormality, usually with onset in childhood. The most common seizure type is complex partial. The characteristic EEG pattern may sometimes resemble centrotemporal spikes characteristic for benign epilepsy of childhood [58]. Seizures are often easy to control and may remit. However, the course of the epilepsy is variable and continuous AED treatment in adult life is not unusual.

Prognosis after withdrawal of AEDs

Many physicians assume that epilepsy in those with learning disability never remits. This is incorrect. In fact, many patients with intellectual deficits have a self-limiting seizure disorder. One important study showed that almost half of adult, mentally retarded patients who had been seizure free for at least 2 years had no recurrences when AEDs were withdrawn [59]. This study refers to patients with a 'diagnosis of epilepsy' rather than 'patients with epilepsy', and epilepsy is often overdiagnosed in severely retarded patients (Table 17.2). Other studies of patients with learning disability and controlled epilepsy confirm the possibility of successful discontinuation of AED treatment in adults, as well as in children. In a large, multicentre AED withdrawal study in patients in remission, the risk of seizure recurrence in patients with delayed development/special schooling was not significantly increased compared with other patients [60]. Specchio and Beghi reviewed 28 studies of discontinuation of AEDs in patients who had been seizure free for 2 years or longer. Intellectual deficits were reported to be present in 19 studies and were found to increase the risk of relapse in eight studies, but not in the remaining. Withdrawal of treatment can also be attempted in patients with cerebral palsy. By multivariate analyses, mental retardation was found to be more important than motor impairment in predicting seizure recurrence [61]. Spastic hemiparesis has been found to be more likely to be associated with seizure recurrence than other forms of cerebral palsy, which predominantly affect white matter [62,63].

Drug withdrawal should be considered in patients with learning disability, as in other patients who attain long-standing seizures remission. Recurrence of seizures in the severely retarded and multiply handicapped group usually carries fewer hazards

and social consequences as these patients are usually accompanied by caregivers at all times.

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18 Emergency Treatment of Seizures and Status Epilepticus

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Epilepsy is, for the most part, self-terminating. On occasions, however, seizures of any type can continue unabated and the seizure disorder is then best considered as a separate entity – status epilepticus. One of the earliest references to status epilepticus can be found in a Babylonian treatise on epilepsy from the middle of the first millennium BC, in which the grave prognosis of this condition was described: 'If the possessing demon possesses him many times during the middle watch of the night, and at the time of his possession his hands and feet are cold, he is much darkened, keeps opening and closing his mouth, is brown and yellow as to the eyes. It may go on for some time, but he will die' [1,2]. There were, however, few references to status epilepticus in the ensuing years. Why this may be so is a matter of speculation; Hunter [3] noted that status epilepticus was rare before the advent of powerful antiepileptic drugs (AEDs), and the consequent risk of drug withdrawal. This is undoubtedly an important cause of status epilepticus, but cannot account for the large number of drug-naive patients presenting with status epilepticus in present times. In the nineteenth century, the entity of status epilepticus was first clearly distinguished among the epilepsies. Calmeil [4] used the term 'etat de mal' and later the term status epilepticus appeared in Bazire's translation of Trousseau's lectures on clinical medicine [5]. From that time status epilepticus was, on the whole, a term used to describe mostly convulsive status epilepticus. It was not until the Marseilles conference in 1962 that status epilepticus was generally recognized to include all seizure types and that the definition was based solely on the persistence of the seizure rather than its form [5]. This is of great importance as it is now apparent that many forms of status epilepticus can result in neuronal damage, although such damage remains most commonly the consequence of tonic–clonic status epilepticus. Although the length of time that a seizure or series of seizures have to continue before being classified as status epilepticus has been a matter of debate and is to an extent arbitrary, most would accept a limit of 30 min [1]. Treatment, however, should begin before this period (see below). The necessity of differentiating status epilepticus from other seizure conditions relates to its high morbidity and mortality.

The term status epilepticus, as used by Gastaut and colleagues, included three entities: generalized status epilepticus, partial status epilepticus and unilateral status epilepticus [7]. This classification is, however, both incomplete and too broad to be clinically useful, and recently more detailed classifications have been proposed [8] (Table 18.1).

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Estimates of the overall incidence of status epilepticus have varied from 10 to 60 per 100 000 person-years, depending on the population studied and the definitions used [1,9–11]. Some studies are likely to have underestimated incidence due to incomplete case ascertainment. The incidence also varies in different ethnic groups; status epilepticus is more common in Afro-Americans than in whites, and it is not clear to what extent this difference is due to genetic or socioeconomic factors. Status epilepticus is also more frequently associated with mental handicap, and with structural cerebral pathology (especially in the frontal areas). In established epilepsy, status epilepticus can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease, and is more common in symptomatic than in idiopathic epilepsy. About 5% of all epileptic adult clinic patients will have at least one episode of status epilepticus in the course of their epilepsy [1,12], and in children the proportion is higher (10–25%) [1,12,13]. Most status epilepticus episodes, however, do not develop in patients with a previous diagnosis of epilepsy, and are often due to an acute cerebral disturbance, emphasizing the importance of identifying and treating the acute precipitant. Infections with fever are a common cause of status epilepticus in children, whilst in adults cerebrovascular accidents (CVAs), hypoxia, metabolic causes and alcohol are the main acute causes [10]. Although the prognosis of status epilepticus is related to aetiology, the prognosis of certain conditions such as stroke may be worse if associated with status epilepticus [14]. The overall mortality for status epilepticus is about 20%, most patients dying of the underlying condition, rather than the status epilepticus itself [1,10]. The mortality is age related, and is much lower in children and higher in the elderly [10]. Permanent neurological and mental deterioration can result from status epilepticus, particularly in young children; the risks of morbidity are greatly increased the longer the duration of the status epilepticus episode [15,16]. Furthermore, status epilepticus can result in chronic epilepsy and, indeed, 43% of those with acute symptomatic status epilepticus have a subsequent unprovoked seizure compared with 13% of those with acute symptomatic seizures [17].

Before describing the particular treatment of the various forms of status epilepticus, it is necessary to have an understanding of status-induced neuronal damage, and drug pharmacokinetics and pharmacodynamics during status epilepticus.

Status epilepticus and neuronal damage

The association of neuronal damage with status epilepticus had been noted in the nineteenth century. In more recent times, postmortem studies of individuals who died during status epilepticus

Table 18.1 Classification of status epilepticus (SE).

SE occurring in the neonatal and infantile epilepsy syndromes
West syndrome
Ohtahara's syndrome
Severe myoclonic encephalopathy of infancy (SMEI; Dravet's syndrome)
SE in other forms of neonatal or infantile epilepsy
SE occurring only in childhood
SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos' syndrome)
SE in other forms of childhood epileptic encephalopathies, syndromes and aetiologies (e.g. ring chromosome X and other karyotype abnormalities, Angelman's syndrome, Rett's syndrome, myoclonic–astatic epilepsy), other childhood myoclonic encephalopathies
Electrical status epilepticus in slow-wave sleep (ESES)
Landau–Kleffner syndrome
SE occurring in both childhood and adult life
Convulsive SE
Tonic–clonic SE
Epilepsia partialis continua
Myoclonic SE in coma (after severe brain injury)
Myoclonic SE
NCSE with epileptic encephalopathy
NCSE in Lennox–Gastaut syndrome
Atypical absence status epilepticus
Tonic status epilepticus
Other forms of NCSE in patients with learning disability or disturbed cerebral development (cryptogenic or symptomatic)
NCSE without epileptic encephalopathy
Typical absence status epilepticus in idiopathic generalized epilepsy
Complex partial status epilepticus
Limbic
Non-limbic
NCSE in the aftermath of tonic–clonic seizures
Subtle status epilepticus (myoclonic SE occurring in the late stage of convulsive SE)
Aura continua with sensory, special sensory, autonomic or cognitive symptoms
SE occurring in late adult life
De novo absence status epilepticus of late onset
Boundary syndromes[a]
Some cases of epileptic encephalopathy
Some cases of coma due to acute brain injury with epileptiform EEG changes
Some cases of epileptic behavioural disturbance or psychosis
Some cases of drug-induced or metabolic confusional state with epileptiform EEG changes

[a] Boundary syndromes are defined as cases in which it is not clear to what extent the continuous epileptiform electrographic abnormalities are contributing to the clinical impairment.
NCSE, non-convulsive status epilepticus.
From ref. 1.

have revealed extensive neuronal damage in the temporal lobes [18]. Furthermore, levels of neurone-specific enolase, a marker of neuronal injury, are elevated immediately following status epilepticus [16], and there have been case reports describing the development of hippocampal atrophy in patients followed with neuroimaging after an episode of status epilepticus [e.g. 19,20]. The interpretation of the human data is, however, confounded by other factors such as aetiology, metabolic compromise and treatment. Animal experiments have thus provided a greater insight into neuronal damage associated with status epilepticus [22]. Initial experiments demonstrated that convulsive status epilepticus resulted in neuronal damage, and that neuronal damage occurred even if the systemic and metabolic compromise that occurs in convulsive status epilepticus was controlled. This led to the concept that it was the presence of ongoing electrographic seizure activity that itself resulted in neuronal damage (excitotoxic neuronal damage) [22,23]. Animal studies of non-convulsive status have shown similar changes [24]. Importantly, this neuronal damage is time dependent, and as such stopping the status epilepticus as soon as possible will prevent much of the damage from occurring.

Tonic–clonic status epilepticus can undoubtedly cause neuronal damage, although the damage is more likely to depend on the site of cerebral origin of the epilepsy, its severity and clinical context. Damage is certainly not invariable, and one encounters some patients who have had severe attacks, prolonged attacks or repeated attacks and who make complete recoveries without noticeable damage. It is important to realize that the animal models were developed to explore excitotoxicity, and caution is needed in extrapolating these findings to the human condition. The animal models used generally involve induction of status epilepticus in a non-epileptic animal with either powerful chemoconvulsants or prolonged high-frequency repetitive stimulation [24–26]. There are rare occurrences of comparable precipitants in humans, such as domoic acid poisoning from mussels, in which pathological changes occurr that are similar to the animal models [18], but these are exceptional. Complex partial status epilepticus (CPSE) in humans, in particular, is very different from that in animal models. CPSE in humans tends to have lower-frequency discharges, which, if reproduced in animal models, produces substantially less neuronal damage [27–30]. In general, it seems that human CPSE is more benign than the experimentally produced CPSE. Most patients recover without any sequelae. There have been reports of prolonged memory problems, hemiparesis and death occurring following CPSE, although, in many of these cases, the outcome relates to the underlying aetiology [31–33]. In one study, only 10 patients were identified with significant morbidity from CPSE over a 10-year period (this almost certainly represents a small fraction of all patients with CPSE during this period) [34]. Furthermore, in seven of these patients, coincident conditions undoubtedly contributed significantly to this morbidity. In many reported cases, aggressive treatment with intravenous therapy and, on occasions, barbiturate anaesthesia could also contribute to the consequent morbidity. Importantly, there have also been large case series of prolonged CPSE with no neurological sequelae [35,36]. Ceiling effects (damage only in the early episodes) in patients with repeated episodes of status also complicate assessment.

One postmortem study has reported substantial neuronal damage following partial status epilepticus in three patients [19]. The aetiology of the status epilepticus is unclear in two cases and the aetiology in the third case was related to carcinomatous meningitis. It is thus difficult to know if the damage is due to the status epilepticus or some unknown pathogenic process (in the two cryptogenic cases, for instance, viral or autoimmune encephalitis).

There are many measurable changes following an episode of status epilepticus, for instance changes in gene expression, recep-

tor trafficking, neurochemical changes, neurophysiological and neuropathological changes (see ref. 37). Rises in serum neurone-specific enolase have also been used as an argument that CPSE results in neuronal damage [38]. These rises could be partially the result of a breakdown in the blood–brain barrier rather than an increase in neuronal death, and cerebrospinal fluid neurone-specific enolase would be a more accurate predictor [39]. The degree to which serum neurone-specific enolase correlates with neurological and cognitive disability in CPSE is especially unclear, since some patients with very high serum neuronal enolase have a good outcome. Neuroimaging in complex partial status has largely also been inconclusive; reversible changes do occur and in some selected patients mild atrophy can be associated with CPSE [40].

Animal evidence also suggests that there may be certain groups who are less prone to neuronal damage from status epilepticus; epileptic animals, animals pretreated with AEDs and young animals are all resistant to chemoconvulsant-induced neuronal damage [41–46]. Thus, young age, AEDs and prior history of epilepsy may all confer neuroprotection.

What is the relationship of this neuronal damage to the subsequent morbidity of status epilepticus? It appears that the neuronal damage that occurs during status epilepticus is not necessary for epileptogenesis [47,48]. Indeed, damaging the hippocampus through severe hypoxic injury seems to inhibit epileptogenesis [49]. The neuronal damage probably more closely relates to other pathologies post status epilepticus such as memory and behavioural problems [47,50].

The main epileptogenic changes following status epilepticus have yet to be clearly defined. Changes have been reported in intrinsic properties of neurones [51], rate of neurogenesis [52], receptor function [53], inhibitory interneurones [54], synaptic arrangements [55] and the extracellular space. All of these could be epileptogenic; however, it has been difficult to identify one critical or necessary process.

Drug pharmacokinetics and pharmacodynamics

In the rational drug treatment of status epilepticus, an understanding of the pharmacokinetics of acutely administered drugs is needed. In particular, it is important to realize three fundamental points: (1) the pharmacokinetics of a drug administered acutely may greatly differ from that of the drug administered chronically; (2) the intracerebral distribution of a drug during a seizure may differ from that in the non-seizure state; and (3) the longer seizures continue the more difficult they are to treat.

Acute drug pharmacokinetics

Fast drug absorption is essential in the treatment of status epilepticus, and thus almost all drugs need to be administered intravenously. Paraldehyde and midazolam, however, may be given intramuscularly, and diazepam and paraldehyde rectally. Other drugs are less commonly given rectally, and midazolam is given by buccal instillation.

In order to act rapidly, the drugs need to cross the blood–brain barrier readily. Drugs achieve this either by being lipid soluble or by having an active transport mechanism. Thus, the drugs that are effective in status epilepticus usually have a high lipid solubility. Thus, they have usually a large volume of distribution.

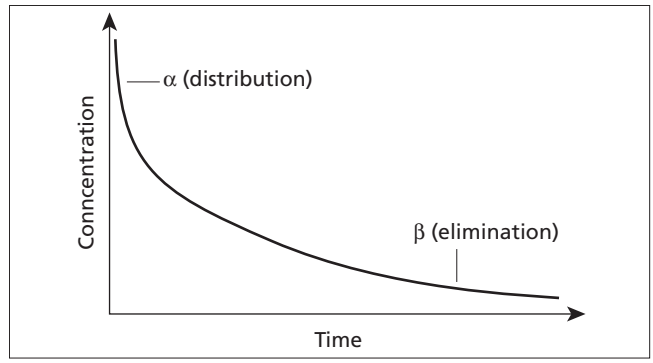

Fig. 18.1 Concentration–time profile of acutely administered drugs showing two phases: a rapid distribution phase (α), in which drug is distributed from the blood compartment to fat and muscle, and a slower elimination phase (β). From ref. 1.

During intravenous (i.v.) administration, a drug directly enters the central compartment (blood and extracellular fluid of highly perfused organs) from where it is distributed to peripheral compartments, in particular fat and muscle. Since most of the drugs with which we are concerned are highly lipid soluble, they are rapidly redistributed into the peripheral compartment from the central compartment. This leads to an initial drop in plasma concentrations, and the rapid fall is measured as the distribution half-life. The drug may be eliminated from the central compartment through renal excretion, hepatic metabolism (the major route of elimination for the majority of AEDs) or exhalation, and the elimination half-life is the measure of this process. The AEDs used in status epilepticus often have a much shorter distribution half-life than elimination half-life (Fig. 18.1). For highly lipid-bound drugs following acute administration, there is a rapid initial fall in plasma levels and brain levels (Fig. 18.1), and thus loss of effect. This has led to the practice of repeat boluses and infusions in order to maintain adequate plasma levels. However, with persistent administration there is accumulation of the drug within the peripheral compartment (saturation), and this results in two important effects [1,56]: (1) higher peak and trough levels with subsequent boluses or with continued infusions; and (2) clearance of the drug from the central compartment becomes dependent on the elimination half-life and therefore it occurs much more slowly (Fig. 18.2). This results suddenly in higher and more persistent drug levels than was the case before saturation occurred.

These two effects are potentially dangerous, and some of the mortality and morbidity of status epilepticus is due to injudicious use of repeated boluses or continuous infusions of lipid-soluble drugs.

Kinetics of drugs during seizures

Seizures (especially convulsive seizures) can affect both peripheral and central pharmacokinetics of drugs. During convulsive seizures, there is a fall in the pH of the blood, resulting in a change in the degree of ionization (and thus lipid solubility) of drugs in plasma. This will affect the distribution half-lives, the ability to cross the blood–brain barrier and the protein binding. In addition, the pH in blood decreases to a greater degree than in the brain; this pH gradient facilitates the movement of a weakly acid

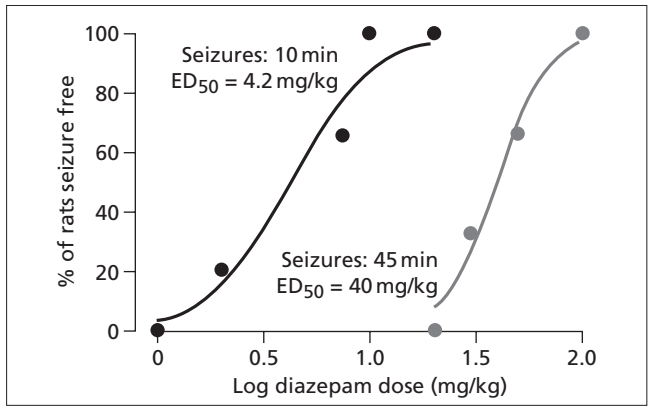

Fig. 18.2 Diazepam was effective in controlling brief (10 min) seizures but lost potency after prolonged (45 min) seizures in a lithium–pilocarpine rat model of status epilepticus. From ref. 58.

drug from blood to brain. This effect can be seen, for instance, with phenobarbital [57]. Other peripheral pharmacokinetic effects are also apparent during status epilepticus. These may result from increased blood flow to muscle, and hepatic and renal compromise (often resulting in a prolongation of the elimination half-life of anticonvulsant drugs). In addition to these peripheral effects, there is also a direct effect of status epilepticus on the brain compartment. There is a breakdown in the blood–brain barrier during convulsive seizures, which again results in more effective brain penetration of anticonvulsant drugs. During seizures there is increased blood flow to seizing brain; thus drugs in which the cortical blood flow determines the rate at which the drug crosses the blood–brain barrier (e.g. phenobarbital) may concentrate in foci of seizure activity in the brain.

Drug responsiveness

As status epilepticus progresses, it becomes more difficult to treat, probably largely because of changes in brain receptors with continued seizure activity [58–62]. Many of the treatments that are successful in the initial stages are ineffective later. Indeed, the potency of benzodiazepines decreases as status epilepticus progresses (Fig. 18.2) [59]; the decrease in their potency is associated with a decrease in the sensitivity of γ-aminobutyric acid (GABA) receptors to benzodiazepines [59]. Acute changes during the episode of status epilepticus must be responsible for the changing responsiveness and, as mentioned above, many neurochemical and neurophysiological changes do occur – often very rapidly. The down-regulation of the benzodiazepine-sensitive $GABA_A$ receptors is probably largely due to seizure-induced changes in the trafficking of receptors from the membrane surface [60,61].

Serial seizures (premonitory phase)

It has been noted that the development of status epilepticus is preceded by an increasing frequency of seizures (a premonitory phase) [1]. Furthermore, as the animal data mentioned above suggests, treatment at this early stage has a much higher chance of success than treatment of established status epilepticus [62]. Treatment at this stage also prevents neuronal damage. Serial seizures and prolonged seizures do not, however, necessarily result in status epilepticus, and in one study of seizures lasting 10–29 min, half the seizures terminated without treatment (whether some of the other episodes that were treated would have terminated without treatment is unknown) [63]. Similarly, a study of new-onset seizures in children found that half the children had seizures lasting longer than 5 min, and 92% of the seizures stopped spontaneously; indeed, approximately three-quarters of the seizures lasting longer than 5 min stopped spontaneously [64]. This introduces two notes of caution: first, that status epilepticus is not an inevitable consequence of prolonged seizures and, second, that treatment studies based on seizures that last less than 30 min may overestimate treatment effects due to spontaneous seizure cessation.

Randomized controlled studies have established the efficacy of oral and rectal diazepam and buccal midazolam in the treatment of serial seizures [65–68]. Most of these studies, however, consider episodes in patient groups (often institutionalized) who have a history of serial seizures but who do not go into status epilepticus. Furthermore, these studies often include many seizure clusters in a few patients. Thus, most of these studies do not directly address the prevention of status epilepticus. However, in a large pragmatic study, buccal midazolam demonstrated superiority over diazepam in a randomized controlled study when given in the emergency room to children [68]. The success rate of either drug was lower than that observed in other studies, perhaps due to their late use (in the emergency room rather than prior to admission), further emphasizing the benefit of early treatment. Buccal midazolam should therefore be preferred to rectal diazepam in children; trial data for buccal midazolam in adults are lacking.

With more prolonged seizures (>10 min) in the community, i.v. diazepam and i.v. lorazepam have been shown to be more effective than placebo at preventing the evolution to, or continuation of, status epilepticus when administered by paramedics [69]. In this study, although not statistically significant, lorazepam had a more impressive effect than diazepam. Interestingly, early treatment in this study did not significantly affect eventual outcome, but this may have been because of the lack of sufficient power in the study to detect such differences (there was a trend to better outcomes for those given active treatment by paramedics) [69].

Rectal paraldehyde has been proposed as an alternative, especially in children. Paraldehyde is, however, difficult to use and administer, and its use should perhaps be reserved for those in whom a rectal benzodiazepine has failed [70].

Tonic–clonic status epilepticus

Diagnosis

Non-epileptic attacks are frequently prolonged and can be confused with status epilepticus. In an audit of patients transferred to a specialist neurological intensive care unit for further treatment of their status epilepticus, approximately half the patients transferred were not in status epilepticus, and were either in pseudostatus or in drug-induced coma (usually secondary to large

amounts of emergency antiepileptic status medication) [71]. The inadequacy of diagnosis from most referring centres was partly due to absent or insufficient EEG services available at those centres. As has been found in another study [72], many patients with pseudostatus had a previous diagnosis of epilepsy that may have confounded the diagnosis. Pseudostatus is often misdiagnosed as true status epilepticus and is often refractory to initial therapy (leading to general anaesthesia and mechanical ventilation) [1,71,72]. Failure by admitting doctors to recognize the possibility of pseudostatus was common. It should thus be emphasized that pseudostatus must be considered if an episode of status epilepticus does not respond promptly to initial therapy (especially if the seizures are in any way atypical).

EEG patterns have also been proposed to be a means of staging the status epilepticus. From experimental models, a progression of EEG changes has been suggested from discrete seizures, to merging seizures, to continuous seizure activity and then eventually periodic lateralized epileptiform discharges (PLEDs) or bilateral periodic epileptiform discharges (BPEDs) [73]. This progression has been proposed to mirror increasing drug resistance and a worsening prognosis [62]. In humans, this clear EEG sequence is not usually found [74]. Although patients with PLEDs generally fare less well, outcome is probably more related to age and aetiology than to any specific ictal pattern [74].

Medical management and complications

Convulsive status epilepticus is a medical emergency because of the significant potential for excitotoxic cerebral damage, other forms of cerebral damage and associated medical complications. The effects of convulsive status epilepticus can be divided into early and late stages. In the early phase, cerebral autoregulation and homeostasis are largely preserved. The initial consequence of a prolonged convulsion is a massive release of plasma catecholamines [75], which results in an increase in heart rate, blood pressure and plasma glucose. During this stage, cardiac arrhythmias are frequently seen, and may be fatal [76]. Cerebral blood flow is greatly increased and thus glucose delivery to active cerebral tissue is maintained [77]. As the seizure continues, there is a steady rise in the core body temperature, and prolonged hyperthermia above 40°C can cause cerebral damage and has a poorer prognosis [78,79]. Acidosis also commonly occurs, and in one series 25% of the patients had an arterial pH below 7.0 [80]. This acidosis is mainly the result of lactic acid production, but there is also a rise in carbon dioxide tension that can, in itself, result in life-threatening narcosis [80]. The acidosis can increase the likelihood of life-threatening cardiac arrhythmias and hypotension and, in conjunction with the cardiovascular compromise, may result in severe pulmonary oedema [81].

The status epilepticus may then enter a second late phase in which cerebral and systemic protective measures progressively fail. The main characteristics of this phase are a fall in blood pressure, a loss of cerebral autoregulation, resulting in the dependence of cerebral blood flow on systemic blood pressure, and hypoglycaemia due to the exhaustion of glycogen stores and the increased neurogenic insulin secretion [75,82,83]. Intracranial pressure may rise precipitously in status epilepticus. The combined effects of systemic hypotension and intracranial hypertension can result in a compromised cerebral circulation and cerebral oedema [84], particularly in children. Further complications may occur, including rhabdomyolysis, leading to acute tubular necrosis, hyperkalaemia and hyponatraemia [85]. Hepatic compromise is not uncommon, and rarely there may be disseminated intravascular coagulation with its subsequent complications [86]. Because of these medical complications, status epilepticus that has lasted an hour or more (and sometimes less) should be managed in the intensive care unit, where there is adequate monitoring and treatment of these potential complications.

Thus, for the new patient presenting as an emergency in status epilepticus, it is helpful to plan therapy in a series of progressive phases – this scheme is taken from Shorvon [1].

First stage (0–10 min)

Oxygen and cardiorespiratory resuscitation

It is first essential to assess cardiorespiratory function, to secure the airway and to resuscitate where necessary. Oxygen should always be administered, as hypoxia is often unexpectedly severe.

Second stage (1–60 min)

Monitoring

Regular neurological observations and measurements of pulse, blood pressure, electrocardiography and temperature should be initiated. Metabolic abnormalities may cause status epilepticus, or develop during its course, and biochemical, blood gas, pH, clotting and haematological measures should be monitored.

Emergency anticonvulsant therapy

This should be started (see below).

Intravenous lines

These should be set up for fluid replacement and drug administration [preferably with 0.9% sodium chloride (normal or physiological saline) rather than 5% glucose solutions]. Drugs should not be mixed and, if two AEDs are needed (e.g. phenytoin and diazepam), two i.v. lines should be sited. The lines should be in large veins, as many AEDs cause phlebitis and thrombosis at the site of infusion. Arterial lines must never be used for drug administration.

Emergency investigations

Blood should be drawn for the emergency measurement of blood gases, sugar, renal and liver function, calcium and magnesium levels, full haematological screen (including platelets), blood clotting measures and anticonvulsant levels. Fifty millilitres of serum should also be saved for future analysis, especially if the cause of the status epilepticus is uncertain. Other investigations depend on the clinical circumstances.

Intravenous glucose and thiamine

Fifty millilitres of a 50% glucose solution should be given immediately by i.v. injection if hypoglycaemia is suspected. If there is a history of alcoholism, or other compromised nutritional states, 250 mg of thiamine (e.g. as the high-potency i.v. formulation of Pabrinex, 10 mL of which contains 250 mg) should also be given

intravenously. This is particularly important if glucose has been administered, as a glucose infusion increases the risk of Wernicke's encephalopathy in susceptible patients. Intravenous high-dosage thiamine should be given slowly (e.g. 10 mL of high-potency Pabrinex over 10 min), with facilities for treating the anaphylaxis, which is a potentially serious side-effect of Pabrinex infusions. Routine glucose administration in non-hypoglycaemic patients should be avoided as there is some evidence that this can aggravate neuronal damage.

Acidosis
If acidosis is severe, the administration of bicarbonate has been advocated in the hope of preventing shock, and mitigating the effects of hypotension and low cerebral blood flow. In most cases, however, this is unnecessary and more effective is the rapid control of respiration and abolition of motor seizure activity.

Third stage (0–60/90 min)

Establish aetiology
The causes of status epilepticus differ with age, and in the presence or absence of established epilepsy. The investigations required depend on clinical circumstances. Computed tomography or magnetic resonance imaging and cerebrospinal fluid examination are often necessary; the latter should be carried out only with facilities for resuscitation available, as intracranial pressure is often elevated in status epilepticus.

If the status epilepticus has been precipitated by drug withdrawal, the immediate restitution of the withdrawn drug, even at lower doses, will usually rapidly terminate the status epilepticus. Pyridoxine should also be given intravenously to children under the age of 3 years who have a prior history of epilepsy and to all neonates.

Physiological changes and medical complications
The physiological changes of uncompensated status epilepticus, listed above, may need specific therapy. Active treatment is most commonly required for hypoxia, hypotension, raised intracranial pressure, pulmonary oedema and hypertension, cardiac arrhythmias, cardiac failure, lactic acidosis, hyperpyrexia, hypoglycaemia, electrolyte disturbance, acute hepatic or renal failure, rhabdomyolysis or disseminated intravascular coagulation.

Pressor therapy
Dopamine is the most commonly used pressor agent, given by continuous i.v. infusion. The dose should be titrated to the desired haemodynamic and renal responses (usually initially between 2 and 5 μg/kg/min, but this can be increased to over 20 μg/kg/min in severe hypotension). Dopamine should be given into a large vein as extravasation causes tissue necrosis. Electrocardiographic monitoring is required, as conduction defects may occur, and particular care is needed in dosing in the presence of cardiac failure.

Fourth stage (30–90 min)

Intensive care
If seizures are continuing in spite of the measures taken above, the patient must be transferred to an intensive care environment, and the usual measures instituted.

Intensive care monitoring
In severe established status epilepticus, intensive monitoring may be required, including intra-arterial blood pressure, oximetry, central venous pressure and pulmonary artery pressure monitoring.

Although magnesium is effective at preventing eclampsia, there is no evidence to suggest that increasing magnesium serum concentrations to supranormal levels has any benefit in status epilepticus. Indeed, such a policy can result in motor paralysis, difficulty in detecting clinical seizure activity and hypotension [87]. However, serum magnesium can be low in alcoholics and patients with acquired immune deficiency syndrome (AIDS) [88,89], and in these patients i.v. loading with 2–4 g of magnesium sulphate over 20 min may help with seizure control and prevention of arrhythmias.

Seizure and EEG monitoring
In prolonged status epilepticus, or in comatose ventilated patients, motor activity can be barely visible. In this situation, continuous EEG monitoring using a full EEG or a cerebral function monitor is necessary, and at the very least intermittent daily EEGs should be recorded. The latter must be calibrated individually, and then can register both burst suppression and seizure activity. Burst suppression provides an arbitrary physiological target for the titration of barbiturate or anaesthetic therapy. Drug dosing is commonly set at a level that will produce burst suppression with interburst intervals of between 2 and 30 s.

Intracranial pressure monitoring and cerebral oedema
Continuous intracranial pressure monitoring is advisable, especially in children, in the presence of persisting, severe or progressive elevated intracranial pressure. The need for active therapy is usually determined by the underlying cause rather than the status epilepticus. Intermittent positive-pressure ventilation, high-dose corticosteroid therapy (4 mg dexamethasone every 6 h), or mannitol infusion may be used (the last is usually reserved for temporary respite for patients in danger of tentorial coning). Neurosurgical decompression is occasionally required.

Long-term anticonvulsant therapy
Long-term, maintenance, anticonvulsant therapy must be given in tandem with emergency treatment. The choice of drug depends on previous therapy, the type of epilepsy and the clinical setting. If phenytoin or phenobarbital has been used in emergency treatment, maintenance doses can be continued orally (through a nasogastric tube) guided by serum level monitoring. Other maintenance AEDs can be started also by giving oral loading doses.

Drug treatment

The doses of drugs commonly used in status epilepticus are contained in Table 18.2. There have been eight randomized studies of i.v. drug treatment in status epilepticus [90–97]. These studies are beset by methodological problems. They use different definitions of status epilepticus, most do not take adequate precautions to exclude patients with pseudostatus epilepticus, and they use different doses of drugs. Also, there are problems of rapid randomization and of defining outcome. These studies compared lidocaine against placebo [94], lorazepam against diazepam [90,92], phenobarbital against diazepam and phenytoin [93],

Table 18.2 Drugs used in the pre-anaesthetic management of status epilepticus.

Drug	Route	Adult dose	Paediatric dose
Diazepam at 2–5 mg/min[a]	i.v. bolus Rectal administration	10–20 mg at 2–5 mg/min[a] 10–30 mg[a]	0.25–0.5 mg/kg 0.5–0.75 mg/kg[a]
Midazolam	i.m. or rectally i.v. bolus i.v. infusion	5–10 mg[a] 0.1–0.3 mg/kg at 4 mg/min[a] 0.05–0.4 mg/kg/h	0.15–0.3 mg/kg[a]
Paraldehyde	Rectally or i.m. i.v.	5–10 mL (approx 1 g/mL) in equal volume of water[a] 5–10 mL/h as a 5% solution in 5% dextrose	0.07–0.35 mL/kg[a]
Chlormethiazole	i.v. infusion of 0.8% solution	40–100 mL at 5–15 mL/min, then 0.5–20 mL/min	0.1 mL/kg/min increasing every 2–4 h
Clonazepam	i.v. bolus	1–2 mg at 2 mg/min[a]	250–500 mg
Fosphenytoin	i.v. bolus	15–20 mg PE/kg at 150 mg PE/min	
Lignocaine	i.v. bolus i.v. infusion	1.5–2.0 mg/kg at 50 mg/min[a] 3–4 mg/kg/h	
Lorazepam	Rectally i.v. bolus	0.05–0.1 mg/kg 0.07 mg/kg (usually 4 mg)a	 0.1 mg/kg
Phenytoin	i.v. bolus/infusion	15–20 mg/kg at 50 mg/min	20 mg/kg at 25 mg/min
Phenobarbital	i.v. bolus	10–20 mg/kg at 100 mg/min	15–20 mg/kg
Valproate	i.v. bolus	15–30 mg/kg	20–40 mg/kg

After ref. 148.
[a]May be repeated.
i.m., intramuscular; i.v., intravenous; PE, phenytoin equivalent.

intramuscular (i.m.) midazolam against i.v. diazepam [91], four different i.v. treatment regimes (lorazepam, phenytoin alone, diazepam and phenytoin, and phenobarbital) [95], valproate against phenytoin [96] and valproate against i.v. diazepam in refractory status epilepticus [97].

Certain conclusions can be drawn from these studies: (a) lidocaine is effective in the treatment of status epilepticus [94]; (b) lorazepam and diazepam are equally effective, although more patients required additional AEDs if given diazepam [90,92]; (c) lorazepam is more effective than phenytoin alone [95]; (d) i.m. midazolam is as effective as initial i.v. diazepam and may be an alternative if i.v. access is difficult in children [91]; (e) phenobarbital alone is as effective as other regimens [93,95]; (f) lorazepam is faster to administer than other drugs; and (g) no particular drug or drug combination has significantly more side-effects including respiratory depression (importantly phenytoin alone was not significantly superior to regimens containing benzodiazepines) [95]. The studies of valproate are unfortunately difficult to interpret. In one study, patients were randomized to valproate or phenytoin alone (an inferior treatment) [96]. This study was underpowered and there was no significant difference between the two treatment arms (the study incorrectly reports one-sided *t*-tests). The other study compared i.v. diazepam infusion against i.v. valproate in status epilepticus refractory to benzodiazepine and phenytoin loading [97]. There was no significant difference between the two treatment arms. Both these studies were inconclusive and used non-standard or inferior comparators, but it appears that high doses of valproate can be effective. Overall, drug choice is perhaps not as important as having a protocol so that satisfactory doses of reasonable drugs are given rapidly; indeed, retrospective studies have found that approximately 70% of patients in status epilepticus are given inadequate doses of antiepileptic medication [71,98].

A protocol for the drug treatment of tonic–clonic status epilepticus

It seems sensible to stage treatment, with less intensive initial therapy requiring less support.

Stage of early status epilepticus

Benzodiazepines are widely accepted as the drugs of choice for initial therapy (see Table 18.2). Of these, i.v. lorazepam is now generally preferred over diazepam as first-line therapy in established status epilepticus. The disadvantage of diazepam is its short redistribution half-life (less than 1 h) and large volume of distribution (1–2 L/kg) [99]. These properties mean that serum and brain concentrations rapidly fall after initial i.v. dosing, leading to potentially high rates of seizure recurrence. Within 2 h of successful treatment with diazepam, over half the patients with status epilepticus relapse [100]. Repeat boluses of diazepam can lead to significant accumulation, prolongation of action and progressively greater peak levels [101]. This may result in cardiorespiratory arrest, and so cannot be recommended. Clonazepam shares many of the pharmacokinetic features of diazepam. It has a similarly rapid brain penetration, short distribution half-life and long elimination half-life. Lorazepam, on the other hand, has a lesser volume of distribution and is less lipid soluble. It enters the brain more slowly, taking up to 30 min to reach peak levels, although therapeutic levels are reached within a few minutes. Its distribution half-life is much longer (2–3 h), and its elimination half-life is shorter (approximately 10–12 h). Its effects, therefore, are longer lasting than are those of diazepam, and for this reason lorazepam is the benzodiazepine of choice in status epilepticus [90,98,99]. Lorazepam should be given as a bolus that can be repeated once after 10 min, at which time phenytoin should be administered. Lidocaine as a bolus followed by an infusion has

Table 18.3 A protocol for the intravenous (i.v.) antiepileptic drug treatment of convulsive status epilepticus (SE) in adults.

Stage of early SE
Lorazepam 4 mg i.v. bolus (can be repeated once)
If seizures continue after 30 min → stage of established SE

Stage of established SE
Phenobarbital i.v. infusion of 10 mg/kg at a rate of 100 mg/min, or
Phenytoin i.v. infusion of 15 mg/kg at a rate of 50 mg/min, or
Fosphenytoin i.v. infusion of 15 mg PE/kg at a rate of 100 mg PE/min
If seizures continue after 30/60 min → stage of refractory SE

Stage of refractory SE
General anaesthesia should be induced with either:
Propofol: i.v. bolus of 2 mg/kg, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/h initially reducing to a dose sufficient to maintain a burst suppression pattern on the EEG (usually 1–3 mg/kg/h)
When seizures have been controlled for 12 h, the drug dosage should be slowly reduced over a further 12 h
or
Thiopental: i.v. bolus of 100–250 mg given over 20 s with further 50-mg boluses every 2–3 min until seizures are controlled, followed by a continuous i.v. infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/h)
When seizures have been controlled for 12 h, the drug dosage should be slowly reduced over a further 12 h
or
Midazolam: i.v. bolus of 0.1–0.3 mg/kg at a rate not exceeding 4 mg/min initially, followed by a continuous i.v. infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 0.05–0.4 mg/kg/h)
When seizures have been controlled for 12 h, the drug dosage should be slowly reduced over a further 12 h
If seizures recur, the general anaesthetic agent should be given again for a further 12 h, and then withdrawal attempted again. This cycle may need to be repeated until seizure control is achieved

From ref. 148.

Table 18.4 Anaesthetics for refractory status epilepticus.

Drug	Adult dose	Comments
Midazolam	0.1–0.3 mg/kg at 4 mg/min bolus followed by infusion at 0.05–0.4 mg/kg/h	Elimination half-life of 1.5 h, but accumulates with prolonged use Tolerance and rebound seizures can be problematic
Thiopentone	100–250 mg bolus over 20 s then further 50 mg boluses every 2–3 min until seizures are controlled. Then infusion to maintain burst suppression (3–5 mg/kg/h)	Complicated by hypotension. It has saturable pharmacokinetics, and a strong tendency to accumulate. Metabolized to pentobarbital. It can also cause pancreatitis, hepatic disturbance and hypersensitivity reaction
Pentobarbital	10–20 mg/kg at 25 mg/min then 0.5–1 mg/kg/h increasing to 1–3 mg/kg/h	As above
Propofol	2 mg/kg then 5–10 mg/kg/h	Large volume of distribution and short half-life. Rapid recovery. Can be complicated by lipaemia, acidosis and rhabdomyolysis especially in children. Rebound seizures with abrupt withdrawal

From ref. 148.

been recommended as an alternative to benzodiazepines in those in whom respiratory depression is a concern [102], but is not now widely used.

Stage of established status epilepticus

If initial benzodiazepine therapy is ineffective, then the patient can be considered to be in established status epilepticus. Phenobarbital or phenytoin (or fosphenytoin) is the drug of choice in this situation (Table 18.3). Phenobarbital is easier to use, and possibly more effective, but phenytoin may be associated with a lower risk of respiratory depression. Controlled studies have not, however, been carried out, and the relative merits of the two therapies are unclear. Intravenous valproate or levetiracetam have also been proposed as alternatives.

Phenytoin is relatively insoluble in water, and its parenteral formulation has a high pH; consequently, it has a number of side-effects related to its physicochemical properties. It may crystallize and precipitate in solutions; it may cause thrombophlebitis (particularly with extravasation); its vehicle, propylene glycol, can cause hypotension; and phenytoin is poorly and erratically absorbed after i.m. injection. Fosphenytoin (3-phosphoryloxymethyl phenytoin disodium) is a water-soluble phenytoin prodrug which has some advantages relating to tolerability over phenytoin [103]. Fosphenytoin is itself inactive, but is metabolized to phenytoin with a half-life of 8–15 min [103]. It can be administered 2–3 times faster than phenytoin and achieves similar mean serum concentrations, although there is considerable scatter of levels. Cardiac monitoring is still required with fosphenytoin, and the dosing units of the drug are confusing and have caused problems in practice in inexperienced emergency units. There are no controlled trials of fosphenytoin in status epilepticus, and it is not clear if the potential tolerability advantages of fosphenytoin overcome the potential variability in phenytoin levels and the difficulties in dosage, translate in practice into a better outcome than that achieved by phenytoin.

Stage of refractory status epilepticus

In most cases of convulsive status epilepticus (over 80%), therapy with benzodiazepine and phenobarbital or phenytoin will control the seizures rapidly. If the seizures are continuing, however, there is a risk of physiological compromise, neuronal damage and progressive drug resistance. This is the stage of refractory status epilepticus, and transfer to an intensive care unit is required [104]. In many emergency situations (e.g. postoperative status epilepticus, severe or complicated convulsive status epilepticus, patients already in intensive care), anaesthesia should be introduced earlier.

The prognosis of status epilepticus at this stage is less good; in one meta-analysis, the mortality at this stage was estimated to be as high as 48%, with only 29% returning to their premorbid functional baseline [105], although the methodology of this meta-analysis has been open to severe criticism, and the actual mortality in normal practice must be considerably lower than this. The mortality is greater in older patients, those with longer seizure duration, those in a poorer medical condition and those with acute brain injury.

Anaesthesia can be induced by barbiturate or non-barbiturate drugs (Table 18.4). A number of anaesthetics have been recommended [104,106]. The most commonly used anaesthetics are the i.v. barbiturates thiopentone or pentobarbital, the i.v. non-barbiturate infusional anaesthetic propofol or continuous midazolam infusion [104,106]. There have been no randomized controlled studies comparing these treatment options. The aforementioned meta-analysis suggests that there is no difference between these anaesthetics in terms of mortality, but that pentobarbitone was perhaps more effective than midazolam at the expense of greater hypotension [106]. These data, however, need to be interpreted with caution, as the studies compared were non-randomized, had different outcome measures and were subject to considerable reporting bias (the reports are mostly retrospective). Propofol and midazolam have pharmacokinetic advantages over the barbiturates, which readily accumulate. In addition to anaesthesia, it is important that oral AED treatment should continue (usually given by nasogastric tube) and failure to do so will result in seizure relapse when the emergency therapy is withdrawn.

It is imperative at this stage to monitor the EEG, as drug-induced coma can occur with little outward sign of convulsions, yet have ongoing electrographic epileptic activity [106,107]. This exposes the patient to excitotoxic seizure-induced cerebral damage. In addition, patients with prolonged convulsive status epilepticus can enter a stage of subtle generalized convulsive status epilepticus characterized by profound coma, bilateral EEG ictal discharges and only subtle motor activity, regardless of the presence or absence of sedating drugs or paralysing agents [108].

The electrographic endpoint for anaesthetic titration is controversial as there are sparse published data on the subject. The titration of the dose of anaesthetic agents in their use in status is commonly based upon burst suppression on the EEG or cerebral function monitor (CFM) with inter-burst intervals of 2–30 s as an acceptable endpoint [109–111]. Burst suppression supposedly represents disconnection of cerebral grey matter from underlying white matter. Burst suppression can be difficult to achieve, because the degree of anaesthesia required commonly leads to hypotension. Aiming for a more realistic endpoint such as seizure suppression, although more difficult to define, may be more acceptable [71]. EEG monitoring should either be continuous or be repeated regularly.

There are case reports of the successful use of newer drugs (such as oral topiramate and i.v./oral levetiracetam) and steroids in refractory status epilepticus; unfortunately, trials of these are still lacking [112].

Once the patient has been free of seizures for 12–24 h, and provided that there are adequate plasma levels of concomitant antiepileptic medication, then the anaesthetic can be slowly tapered. If seizures recur, the anaesthetic should be reinstated. If one anaesthetic agent is ineffective then it should be replaced by another. There are some data to suggest that those who are loaded with phenobarbital do better than those who are not [12]. In severe cases, anaesthesia may be required for weeks or even months, with many cycles of attempted anaesthetic withdrawal and reinstatement. Eventual recovery occurs in many patients, even after very prolonged episodes, and the process of maintaining a patient under anaesthetic for weeks or months requires great skill, in view of the attendant risks. The ultimate outcome is worse the longer the status continues, but even after very prolonged attacks, a complete recovery can occur. Much depends on the underlying cause – and the ultimate prognosis is more dependent on this than on the duration of seizures.

The above schema is for a typical case, but obviously there are situations in which management will vary considerably. For instance, status epilepticus in the immediate post-neurosurgery or post-head injury situation should be managed by immediate anaesthesia. Similarly, status epilepticus in patients with pre-existing epilepsy due to drug withdrawal should be treated with immediate reinstatement of the withdrawn drug, parenterally if possible. Status in infants and young children can also require a different approach, outlined elsewhere.

Non-convulsive status epilepticus

The advent of more widely accessible EEG and, in particular, the availability of EEG on intensive care units has led to the recognition that non-convulsive status epilepticus (NCSE) is a much more common condition than previously recognized. Indeed, indirect estimates for the incidence of NCSE have been as high as 14–24 per 100 000 population per year (the majority of these are NCSE in the setting of learning difficulties) [6]. Population studies have demonstrated that NCSE accounts for at least one-third of all cases of status epilepticus [9]. NCSE comprises different syndromes, which require different treatment (Table 18.1) [113]. Here, we consider the therapy of typical absence status epilepticus, CPSE, NCSE in coma and specific forms of status epilepticus in patients with learning difficulties, including tonic status epilepticus and atypical absence status epilepticus.

Diagnosis

The diagnosis of NCSE is critically dependent on EEG. In patients with a previous diagnosis of epilepsy, any prolonged change in personality, prolonged postictal confusion (greater than 30 min) or recent-onset psychosis should be investigated with EEG as these can all be presentations of NCSE [114–116]. If progressive developmental delay occurs in the setting of epilepsy, then a sleep EEG should be considered to identify status epilepticus during slow-wave sleep. In non-comatose patients with no history of epilepsy, NCSE can present as confusion or personality change, but almost invariably in the setting of a metabolic derangement, encephalitis or other acute precipitant. Rarely, NCSE can present as autism, and if suspicions are raised (usually a fluctuating course) then EEG is indicated [117,118].

Non-convulsive status epilepticus can result from convulsive status epilepticus, and is an important, treatable cause of persistent coma following convulsive status epilepticus [114,119]. This, and status epilepticus with subtle manifestations such as twitching of the limbs or facial muscles or nystagmoid eye jerking, which can result from hypoxic brain damage, are often collectively referred to as subtle motor status epilepticus [108]. Up to 8% of patients in coma who have no outward signs of seizure activity are in NCSE, thus emphasizing the importance of EEG in the investigation of comatose patients [120]. Similarly, NCSE is underdiagnosed in the confused elderly, in whom the confusion is frequently blamed on other causes [121,122].

Although EEG interpretation is usually straightforward, with regular repetitive discharges occurring in some patients in a cyclical fashion, difficulties can occur in differentiating NCSE from an encephalopathy of other cause [123]. Triphasic waves due to metabolic encephalopathies (particularly hepatic or hyperammonaemic) can be frequent and occasionally sharpened, leading to confusion. Thus, definitions of NCSE should include either (a) unequivocal electrographic seizure activity; (b) periodic epileptiform discharges or rhythmic discharge with clinical seizure activity; or (c) rhythmic discharge with either clinical or electrographic response to treatment [123]. Although these definitions are helpful, difficulties can still arise; triphasic waves can respond to treatment with benzodiazepines, and thus response to treatment is not a definitive indication of an epileptic cause [124]. There is also uncertainty about the relevance of PLEDs [125]. This is most notable following severe encephalitis or hypoxic injury in which discharges can occur with such periodicity so as to be confused with periodic discharges seen following prolonged status epilepticus. Some have argued that such discharges represent ongoing seizure activity, and should be treated thus. The general consensus, however, is that a multitude of aetiologies can underlie PLEDs, and that they should be treated as epileptic only if there is other evidence of ictal activity [125].

Table 18.5 Treatment of different types of non-convulsive status epilepticus (NCSE).

Type	Treatment choice	Other drugs that can be used
Typical absence status epilepticus	i.v. or oral benzodiazepines	Acetazolamide, valproate or chlormethiazole
Complex partial status epilepticus	Oral clobazam	i.v. lorazepam and phenytoin (fosphenytoin) or phenobarbital
Atypical absence status epilepticus	Oral valproate	Oral benzodiazepines (with caution), lamotrigine, topiramate
Tonic status epilepticus	Oral lamotrigine	Methylphenidate, steroids
Myoclonic status epilepticus in coma	Barbiturate anaesthesia (for short trial period)	Steroids, midazolam
Other forms of myoclonic status epilepticus	Oral valproate, benzodiazepines	Levetiracetam
Epilepsia partialis continua	Any oral anticonvulsant	Steroids, immunosuppression
NCSE in the aftermath of tonic–clonic seizures	i.v. benzodiazepines	i.v. phenytoin or phenobarbital
Subtle status epilepticus	Anaesthesia	Steroids

Medical management

Typical absence status epilepticus

This term should be reserved for prolonged absence attacks with continuous or discontinuous 3-Hz spike and wave occurring in patients with primary generalized epilepsy [6]. There are borderline cases also, in which the EEG can include irregular spike–wave, prolonged bursts of spike activity, sharp wave or poly-spike and wave, and it is not clear how to classify these cases.

There is also a category of absence status epilepticus which occurs *de novo* in late adult life [6,126,127] (*de novo* absence status epilepticus of late onset). This often follows drug or alcohol withdrawal and there may or may not be a history of idiopathic generalized epilepsy [6,128].

There is no evidence that absence status induces neuronal damage, and thus aggressive treatment is not warranted [6,128]. Treatment can either be i.v. or oral (Table 18.5). Absence status epilepticus responds rapidly to i.v. benzodiazepines; there is no good evidence to favour one benzodiazepine over another. Sodium valproate is one of the alternatives.

Complex partial status epilepticus

Complex partial status epilepticus (CPSE) has to be differentiated from other forms of NCSE, from postictal states and from other neurological and psychiatric conditions. EEG may be helpful, but the scalp EEG changes can be non-specific and the diagnosis has to be largely clinical [1,31]. The definition as 'a prolonged epileptic episode in which focal fluctuating or frequently recurring electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms' [1] emphasizes that complex partial status epilepticus can originate in any cortical region and can fluctuate in a cyclical fashion [6]. The differentiation of CPSE from generalized NCSE can be difficult, as rapid generalization can occur despite an initial focus that may only become apparent after treatment [30,129].

How aggressively CPSE needs to be treated depends upon (a) the prognosis of the condition and (b) if treatment improves the prognosis. As in all epilepsies, the prognosis relates partly to the prognosis of the underlying aetiology and any concomitant medical conditions. Indeed, CPSE in someone with epilepsy is a more benign condition than complex status epilepticus resulting from an acute cerebral event, and should perhaps be treated thus [35]. There is no good evidence that aggressive treatment improves prognosis in this condition; it is important to note that i.v. medication can result in hypotension, respiratory depression and occasionally cardiorespiratory arrest. Indeed, in one series of NCSE in the elderly, aggressive treatment carried a worse prognosis than no treatment [122]. At present, early recognition of the condition and treatment with oral or rectal benzodiazepines can be effective. Valproate may be an alternative, as i.v. valproate is well tolerated with little respiratory or cardiac depression; trials are urgently needed in this area. In patients who have repetitive attacks of CPSE (a common occurrence), oral clobazam over a period of 2–3 days, given early at home, can usually abort the status epilepticus, and such strategies should be discussed with the patient and carers [130,131]. Early recognition is a critical goal, as the delay in treatment comes not from therapeutic strategy, but from failure to diagnose the condition in the first place. For more persistent or resistant CPSE, i.v. therapy should perhaps be used (see Table 18.5), and lorazepam followed by phenytoin (or fosphenytoin) are the drugs of choice [132]. In contrast to

absence status epilepticus, the response to benzodiazepines can be disappointing, and often there is a resolution of the electrographic status epilepticus without concomitant clinical improvement (possibly due to postictal effects) [35]. Whether general anaesthesia is ever justified remains a matter for speculation. Since most CPSE is self-terminating, usually without any serious neurological sequelae, then such aggressive therapy should, in most instances, be avoided. Treatment of the underlying cause (e.g. encephalitis or metabolic derangement) is, of course, paramount.

Atypical absence status epilepticus

Atypical absence status epilepticus is a form of absence status epilepticus associated with the epileptic encephalopathies such as Lennox–Gastaut syndrome [1]. This entity can be difficult to diagnose, but should be considered if there is a change in behaviour, personality, cognition or increased confusion in a patient with one of these epilepsies. The episodes can be prolonged (going on for hours, days or even longer) and the patient may drift in and out of atypical absence status without a clear onset or offset. The EEG characteristics are usually that of continuous or frequent slow (<2.5 Hz) spike and wave. The EEG changes during these periods of absence status can be subtle, and rather similar to the baseline EEG. This condition is usually poorly responsive to i.v. benzodiazepines, which should, in any case, be given cautiously, as they can induce tonic status epilepticus in susceptible patients [133]. Oral rather than i.v. treatment is usually more appropriate, and the drugs of choice are valproate, lamotrigine, clonazepam, clobazam and topiramate (see Table 18.5). Sedating medication, carbamazepine and vigabatrin have been reported to worsen atypical absences.

Tonic status epilepticus

Tonic status epilepticus is not uncommon in patients with syndromes such as Lennox–Gastaut. Tonic status epilepticus can also rarely occur in the setting of normal premorbid intelligence [134]. The tonic seizures may not necessarily be clinically apparent; the EEG, however, demonstrates bursts of paroxysmal, generalized fast discharges [134,135]. Tonic status epilepticus is poorly responsive to conventional treatment. It can be worsened with benzodiazepines, which should be used with care [133]. Sedating medication can worsen all seizure types in Lennox–Gastaut syndrome, and thus should be avoided. Conversely, stimulants such as methylphenidate can be effective. There has also been a case report of the effective termination of tonic status epilepticus with oral lamotrigine [136]. In Lennox–Gastaut syndrome, both adrenocorticotropic hormone (ACTH) and corticosteroids are helpful in the emergency treatment of status epilepticus of all types.

Subtle status epilepticus

This is a clinical and EEG situation similar to that of myoclonic status epilepticus in coma (see below), which can occur in the late stage of convulsive status epilepticus, if untreated, and in this situation is known as subtle status epilepticus [137]. In contrast to the situation in myoclonic status epilepticus in coma, this undoubtedly represents seizure activity and should be treated aggressively with deep anaesthesia and concomitant AEDs (see Table 18.5).

Non-convulsive status epilepticus in the aftermath of tonic–clonic seizures

Non-convulsive status epilepticus can occur in the aftermath of convulsive seizures, in which there may be prolonged confusion with minimal or no motor activity. The EEG shows ongoing electrical activity [114,119]. The recommended treatment is with i.v. benzodiazepines.

Epilepsia partialis continua

This can be considered the status equivalent of simple partial motor seizures, and can be defined as regular or irregular clonic muscular twitching affecting a limited part of the body, occurring for a minimum of 1 h, and recurring at intervals of no more than 10 s [138]. It needs to be differentiated from myoclonic dystonia and brainstem myoclonus. Diagnosis can be difficult; the EEG may show focal abnormalities, but can be normal [138,139]. Epilepsia partialis continua can result from structural abnormalities such as stroke, trauma, cerebral infarction, cerebral abscess, neuronal migration disorders and vascular malformation [138–141]. In approximately 50% of cases, the magnetic resonance imaging scan is normal [139]. Epilepsia partialis continua can be associated with a variety of encephalitides, commonly Rasmussen's encephalitis, but also subacute panencephalitis and Creutzfeldt–Jakob disease [139,141]. It is also not uncommon in the autoimmune encephalopathies. Metabolic causes have also been described, including, importantly, hyponatraemia and hyperglycaemia, although the majority of such patients also have a focal cortical lesion [142]. Treatment is best targeted at the underlying cause. AEDs may prevent seizure spread into complex partial and secondary generalized seizures, but are usually only partially effective in treating the epilepsia partialis continua [139]. Oral corticosteroid therapy and immunosuppression can be of benefit to patients with chronic inflammatory (e.g. Rasmussen's encephalitis) or autoimmune conditions, and nimodipine has been reported to have been successful in two cases of epilepsia partialis continua following an acute cerebral event [143]. Neurosurgical resection should be considered in refractory cases.

Myoclonic status epilepticus in coma

This diagnosis is made in patients who have suffered severe brain injury (for instance, cerebral anoxia following cardiac arrest) who are in deep coma, sometimes with subtle myoclonic twitching, in whom the EEG shows PLEDs or BPEDs, periodic discharges and encephalopathic triphasic patterns or burst suppression patterns [144]. This situation is not uncommon and is seen in up to 8% of patients in coma with no clinical evidence of seizure activity [120]. This is often an agonal event and the prognosis is usually extremely poor, although survival can occur especially if the initial insult was primarily hypoxia related [145]. Survivors are usually left with Lance–Adams-type action myoclonus, which in itself can have a good prognosis [146]. Whether the EEG changes represent electrographic status epilepticus is contentious, and our view is that these usually simply indicate underlying widespread cortical damage or dysfunction. To what extent this myoclonic status epilepticus in coma should be treated is a matter of contention. It is our practice to treat aggressively for 12 h with anaesthesia, but if this is not effective in controlling the EEG therapy should be withdrawn [147].

Other forms of myoclonic status epilepticus

Myoclonic status in the progressive myoclonic epilepsies and in primary generalized epilepsy do not usually require i.v. therapy, although if needed, an i.v. benzodiazepine can be given. The preferred therapy is with oral valproate, clonazepam or piracetam.

Drugs most commonly used in status epilepticus

Diazepam

Diazepam is useful in the premonitory or early stages of status. There is extensive clinical experience in adults, children and the newborn; the drug has well-proven efficacy in many types of status, a rapid onset of action, and well-studied pharmacology and pharmacokinetics. It can be given by rectal administration, and the rectal tubule is a convenient rectal preparation. Diazepam has two important disadvantages, however, which limit its usefulness in status. First, although it has a rapid onset of action, it is highly lipid soluble and thus has a short duration of action after a single injection. This means that there is a strong tendency for seizures to relapse after initial control. Secondly, diazepam accumulates on repeated injections or after continuous infusion, and this accumulation carries a high risk of sudden respiratory depression, sedation and hypotension. Furthermore, in occasional patients, very low doses of diazepam cause severe respiratory depression. Other disadvantages are its dependency on hepatic metabolism and the formation of an active metabolite, which can complicate prolonged therapy. Diazepam has a tendency to precipitate from concentrated solutions and to interact with other drugs, and is absorbed onto plastic on prolonged contact.

Usual preparations

Intravenous formulation

Diazepam solution, 2-mL ampoule containing 5 mg/mL, or diazepam emulsion (Diazemuls®), 1-mL ampoule containing 5 mg/mL.

Rectal formulation

A 2.5-mL rectal tube (Stesolid® containing 2 mg/mL) or, alternatively, the same solution utilized for i.v. administration (2-mL ampoule containing 5 mg/mL).

Usual dosage

Intravenous bolus (undiluted) 10–20 mg (adults) or 0.25–0.5 mg/kg (children), at a rate not exceeding 2–5 mg/min. The bolus dosing can be repeated. Rectal administration 10–30 mg (adults) or 0.5–0.75 mg/kg (children), and this can be repeated.

Fosphenytoin

Fosphenytoin is a prodrug of phenytoin. It is converted in the plasma into phenytoin by widely distributed phosphatase enzymes. The half-life of conversion is about 15 min, and conversion is not affected by age, hepatic status or the presence of other drugs. Fosphenytoin is water soluble and prepared in a Tris buffer; it thus causes less thrombophlebitis when given intravenously. It can also be administered intramuscularly. Fosphenytoin itself is inert, and its action in status is entirely due to the derived phenytoin. When fosphenytoin is infused at 100–150 mg phenytoin equivalents (PEs)/min, the rate at which free phenytoin levels are reached in the serum is similar to that achieved by a phenytoin infusion of 50 mg/min (15 mg PE of fosphenytoin is the same as 15 mg of phenytoin). These are mean results and there is considerable scatter, the clinical consequences of which are not known. Fosphenytoin can therefore be administered three times faster than phenytoin, with equivalent risks of hypotension, cardiac arrhythmias and respiratory depression. Its rate of antiepileptic action is also similar. The dosing (in units of PEs) is confusing and has been reported to have been misunderstood in the emergency situation. The lower incidence of local side-effects is a potential advantage over phenytoin, but in other ways the two drugs are equivalent, and fosphenytoin is more expensive.

Usual preparation

Fosphenytoin is formulated in a Tris buffer at physiological pH. Phials of 50 mg PE are available for mixture with dextrose or saline.

Usual dosage

Fosphenytoin is given at a dose of 15 mg PE/kg at a rate of 100–150 mg PE/min (an average adult dose of 1000 mg PE in 10 min).

Lorazepam

Lorazepam is the drug of choice in the early stage of status, given by i.v. bolus injection. A single injection is highly effective, and the drug has a longer initial duration of action and a smaller risk of cardiorespiratory depression than diazepam. There is little risk of drug accumulation, and also a lower risk of hypotension. The main disadvantage of lorazepam is a stronger tendency for tolerance to develop, the drug being usually effective for about 12 h only. It is thus usable only as initial therapy, and longer-term maintenance AEDs must be given in addition. There is a large clinical experience in adults, children and the newborn, with well-proven efficacy in tonic–clonic and partial status, and the pharmacology and pharmacokinetics of the drug are well characterized. Lorazepam is a stable compound which is not likely to precipitate in solution, and is relatively unaffected by hepatic or renal disease. It has the disadvantage of not being available in many countries.

Usual preparation

A 1-mL ampoule containing 4 mg/mL for i.v. injection.

Usual dosage

Intravenous bolus of 0.07 mg/kg (usually 4 mg), repeated after 10 min if necessary (adults); bolus of 0.1 mg/kg (children). The rate of injection is not crucial.

Midazolam

Midazolam is another benzodiazepine which can be used in the premonitory or early stages of status. It is a water-soluble compound, the ring structure of which closes when in contact with serum to convert it into a highly lipophilic structure. Its water solubility provides one major advantage over diazepam, in that it can be rapidly absorbed by i.m. injection or by intranasal or buccal administration. It is therefore useful in situations in which i.v. administration is difficult or ill-advised. Blinded comparisons

with diazepam after i.m. and buccal administration show it to be equivalent in efficacy and speed of action. Although there is a danger of accumulation on prolonged or repeated therapy, this tendency is less than with diazepam. There is, however, only limited published experience in adults or children with status. Occasionally, severe cardiorespiratory depression occurs after intramuscular administration, and other adverse effects include hypotension, apnoea, sedation and thrombophlebitis. Like diazepam, the drug is short acting, and there is a strong tendency for seizures to relapse after initial control. Its half-life is prolonged in hepatic disease or in the elderly. There are also encouraging reports of the use of i.v. infusions of midazolam as an anaesthetic in the refractory stage of status, and midazolam is the only benzodiazepine which should be used as a continuous infusion. With more experience, i.v. midazolam may become the drug of choice for anaesthesia in refractory status.

Usual preparation

A 5-mL ampoule containing 2 mg/mL midazolam hydrochloride.

Usual dosage

Intramuscularly or rectally 5–10 mg (adults); 0.15–0.3 mg/kg (children). This can be repeated once after 15 min. An i.v. bolus of 0.1–0.3 mg/kg may be given at a rate not to exceed 4 mg/min, which can be repeated once after 15 min. An i.v. infusion can be given at a rate of 0.05–0.4 mg/kg/h. Buccal instillation of 10 mg can be given by a syringe and catheter in children or adults.

Phenobarbital

Phenobarbital is one of the drugs of choice in the stage of established status. It is a reliable AED, with well-proven effectiveness in tonic–clonic and partial status, and there is extensive clinical experience in adults, children and in neonates. Phenobarbital has a stronger anticonvulsant action than other barbiturates and an additional potential cerebral protective action. It has a rapid onset and long-lasting action, and can be administered much faster than can phenytoin. Its safety at high doses has been established, and the drug can be continued as chronic therapy. The disadvantages of the drug relate to prolonged use, where because of the long elimination half-life, there is a risk of drug accumulation and inevitable sedation, respiratory depression and hypotension. Marked autoinduction may also occur. It is also a drug not used much in long-term therapy in epilepsy, and when given in status epilepticus will need a long withdrawal period once the episode of status epilepticus is over.

Usual preparation

A 1-mL ampoule containing phenobarbital sodium 200 mg/mL in propylene glycol 90% and water for injection 10%.

Usual dosage

The i.v. loading dose in adults is 10 mg/kg at rate of 100 mg/min (usual adult dose 600–800 mg), followed by maintenance dose of 1–4 mg/kg (adults). For neonates and children, the i.v. loading dose of 15–20 mg/kg is followed by a maintenance dose of 3–4 mg/kg. Higher doses can be given, with monitoring of blood concentrations.

Phenytoin

Phenytoin is a drug of choice and a highly effective medication for the stage of established status. Extensive clinical experience has been gained in adults, children and neonates, and phenytoin has proven efficacy in tonic–clonic and partial status. The drug has a prolonged action, with a relatively small risk of respiratory or cerebral depression and no tendency for tachyphylaxis. Its main disadvantage is the time necessary to infuse the drug and its delayed onset of action. However, the phenytoin prodrug fosphenytoin (see above) can be administered more quickly. The pharmacokinetics of phenytoin are problematic, with Michaelis–Menten kinetics at conventional dosages and wide variation between individuals. Toxic side-effects include cardiac rhythm disturbances, thrombophlebitis and hypotension. The risk of cardiac side-effects is greatly increased if the recommended rate of injection is exceeded, and cardiac monitoring is advisable during phenytoin infusion. There is a risk of precipitation if phenytoin is diluted in other solutions than 0.9% saline or if mixed with other drugs.

Usual preparations

A 5-mL ampoule containing 250 mg stabilized in propylene glycol, ethanol and water (alternatives exist, e.g. phenytoin in a Tris buffer or in infusion bottles containing 750 mg in 500 mL of osmotic saline).

Usual dosage

In adults, a 15–18 mg/kg i.v. infusion can be given via the side arm of a drip or preferably directly via an infusion pump at a rate not exceeding 50 mg/min (20 mg/min in the elderly). In children, a 20 mg/kg i.v. infusion is usually given, at a rate not exceeding 25 mg/min. The drug should never be given by i.m. injection as absorption is erratic and extremely slow.

Propofol

Propofol is the anaesthetic agent of choice for non-barbiturate infusional anaesthesia in status. It is an excellent anaesthetic with very good pharmacokinetic properties. In status, it has a very rapid onset of action and rapid recovery. There are few haemodynamic side-effects, and the drug has been used at all ages. There is, however, only limited published experience of its use in status, or indeed of prolonged infusions. Unlike isoflurane, it is metabolized in the liver and affected by severe hepatic disease. As with all anaesthetics, its use requires assisted ventilation, intensive care and intensive care monitoring. A particular risk is the propofol infusion syndrome, which is a term used to describe the occurrence of hyperkalemia, lipaemia, metabolic acidosis, myocardial failure, renal failure and rhabdomyolysis. It occurs usually on long-term infusion (>48 h) but has been reported even after only 5 h of infusion. It is much more common in young children (and indeed for this reason the use of propofol is relatively contraindicated in children). The syndrome is often fatal. It may be caused by drug-induced impairment of oxidation of fatty acid chains and inhibition of oxidative phosphorylation in the mitochondria, especially in the presence of high catecholamine and cortisol levels. Involuntary movements (without EEG change) can occur, and should not be confused with seizure activity. Rebound seizures are a problem when it is discontinued too rapidly, and a decremental rate of 1 mg/kg every 2 h is recommended when the drug is to be withdrawn.

Usual preparation
A 20-mL ampoule containing 10 mg/mL (i.e. 200 mg) as an emulsion.

Usual dosage
A 2 mg/kg bolus, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/h initially, reducing to 1–3 mg/kg/h. When seizures have been controlled for 12 h, drug dosages should be slowly tapered over 12 h.

Thiopentone/pentobarbital
Thiopentone is, in most countries, the usual choice for barbiturate anaesthesia. It is a highly effective AED, with additional potential cerebral protective action. It reduces intracranial pressure and cerebral blood flow, has a very rapid onset of action, and there is wide experience of its use. The drug has a number of pharmacokinetic disadvantages including saturable kinetics, a strong tendency to accumulate and a prolonged recovery time after anaesthesia is withdrawn. Indeed, severe sedation commonly lasts for days after a thiopental infusion, because of its tendency to accumulate and its slow clearance. Serum concentration monitoring of the parent drug and its active metabolite (pentobarbital) is advisable on prolonged therapy. There is often some tachyphylaxis to its sedative and, to a lesser extent, its anticonvulsant properties. Respiratory depression and sedation is inevitable, and hypotension is common. Other less common side-effects include pancreatitis, hepatic dysfunction and spasm at the injection site. Full intensive care facilities with artificial ventilatory support and intensive EEG and cardiovascular monitoring are needed. It can react with co-medication, and with plastic giving sets, and is unstable when exposed to air. Autoinduction occurs, and hepatic disease prolongs its elimination.

Usual preparations
Injection of thiopentone sodium 2.5 g diluted in 100 mL, and 5 g in 200 mL diluent, to make 100 mL and 200 mL of a 2.5% solution. Thiopentone sodium is also available as 500-mg and 1-g phials to make 2.5% solutions.

Usual dosage
A bolus of 100–250 mg i.v. given over 20 s, with further 50-mg boluses every 2–3 min until seizures are controlled, followed by a continuous i.v. infusion to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/h). The dose should be lowered if systolic blood pressure falls below 90 mmHg despite cardiovascular support. Thiopentone should be slowly withdrawn 12 h after the last seizure.

Valproate
There is a long history of the use of valproate in status epilepticus because early on it was available as an i.v. formulation. However, only recently have randomized trials demonstrated potential as a treatment in status epilepticus, although these trials are inconclusive and used inferior or inappropriate comparators. The theoretical advantages of valproate are a low incidence of respiratory and cardiac depression (there are potentially major advantages), but other potential side-effects such as prolonged bleeding time, hepatic dysfunction, pancreatitis and hyperammonaemia have not been adequately assessed in large studies. Valproate should be avoided in patients with hepatic or mitochondrial disease.

Usual preparations
Injection of thiopentone sodium 2.5 g diluted in 100 mL, and 5 g in 200 mL diluent, to make 100 mL and 200 mL of a 2.5% solution. Thiopentone sodium is also available as 500-mg and 1-g phials to make 2.5% solutions.

Usual dosage
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19 Traumatic Brain Injury and Other Risks

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Introduction: the importance of prevention

The treatment of epilepsy has been focused on the treatment of seizures since epilepsy was first recognized as a disorder of the brain. This is in contrast to most other topic areas in medicine, in which the prevention of the disease is the focus of research and treatments, rather than simply the amelioration of symptoms. In recent years, the attention of scientists and clinicians has shifted somewhat to the investigation of the process of epileptogenesis and, to a more limited extent, towards the development of strategies to prevent epilepsy in those clearly at risk. This is particularly important for epilepsy as, at the present time, our ability to actually 'cure' someone who has already developed epilepsy is quite limited. Therefore, once an individual develops epilepsy, it is likely to be a condition that will persist throughout life. Even for those whose seizures are controlled with medication, it is uncommon to have no side-effects from the treatment. Moreover, individuals with epilepsy have problems beyond the seizures themselves (e.g. depression, cognitive impairment, endocrine dysfunction), which may remain unaffected by antiepileptic drugs (AEDs). Thus, prevention of this entire spectrum of the disorder is much more preferable than trying to treat the symptoms in a piecemeal, and often ineffective, manner.

Who is most at risk?

Identification of those at risk has not been a problem in many areas. There are a number of well-known risk factors with fairly predictable probabilities. Brain 'injury' is a category of risks that can be divided into different subgroups. One can examine traumatic brain injury, which will be the main thrust of this chapter, or can include several other 'injuries', such as neurosurgical procedures, stroke, status epilepticus, infections (both meningitis and encephalitis), the presence of mass lesions, and even chronic neurodegenerative diseases. In addition, since this chapter is focused on prevention, one can examine the known risks associated with primary genetic disorders, both those that are manifest by epileptogenic structural lesions, such as tuberous sclerosis (TS), or those commonly considered as 'channelopathies', such as the families of primary generalized epilepsies. These are conditions that can be identified before the development of epilepsy, and thus, at least theoretically, would be amenable to a prevention strategy.

One of the authors (Dichter) has proposed that we identify a new syndrome, the *RED syndrome*, i.e. the syndrome of risk of epilepsy development. Once we recognize this syndrome, we can identify individuals who clearly have the RED syndrome, such as those with moderate or severe traumatic brain injury (TBI), or young children with TS, and recognize that they need treatment for the RED syndrome in order to prevent the progression to epilepsy. Of course, we first need to develop appropriate treatments, but until we, as a community, agree on the nature of the problem, it is unlikely that we will find appropriate solutions.

What are the risks? Among the most well-characterized risks is TBI. Moderate to severe TBI, with either blood in or around the brain, or a penetrating brain injury, carries a risk of ~30% in the civilian population and as high as 50% in military populations [1–4]. Less severe TBI is associated with a lower risk, but it is only with very mild TBI that the risk is below 3–5%. Spontaneous intracerebral haemorrhage, without associated TBI, is associated with a 8–13% risk [5,6] of developing epilepsy over 5 years. The risk after ischaemic stroke has been more difficult to quantify, possibly because ischaemic strokes can occur in many different parts of the brain, some of which are clearly epileptogenic, whereas others have a very low risk (e.g. brainstem strokes). Most estimates would put the risk at somewhere between 5% and 25%, depending on the type of ischaemic stroke, its location and the duration of the follow-up studies [7,8], although others suggest a risk as low as 3% [9]. Interestingly, a large number of stroke intervention clinical trials have been implemented over the last 25 years, with probably tens of thousands of patients enrolled. As far as can be determined, none of these trials has followed patients long enough to determine what the short-, intermediate- and long-term risks for subsequent development of epilepsy might be in this well-characterized population.

After an episode of status epilepticus, the risk of subsequent epilepsy probably approaches 50% [10]. In this population, it is

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difficult to separate those who might already have developed epilepsy, and for whom the episode of status was their 'first' seizure, from those who developed status for some other reason and then went on to develop chronic epilepsy. In addition, it is not uncommon for an individual who presents in status to be diagnosed with 'encephalitis' based on a few cells and high protein in the cerebrospinal fluid (CSF), both of which might be a consequence of the prolonged seizures rather than evidence of an infectious process. Of interest, it is well established that normal animals who experience a bout of prolonged status epilepticus will develop brain injury and epilepsy over time, so it is quite plausible that otherwise 'normal' humans who develop, for whatever reason, a bout of prolonged seizures may develop chronic epilepsy as a result.

In children with febrile seizures, it is commonly believed that isolated, brief, generalized seizures in the presence of high fevers or ascending fevers represent a benign condition and are not a significant risk factor for subsequent development of epilepsy. On the other hand, focal seizures, prolonged or repetitive seizures, or a combination thereof, are associated with significant risks of subsequent epilepsy, which may be as high as 50% for a child with prolonged focal seizures [11]. A major question associated with these data is whether a child who experiences this kind of 'febrile' seizure had a pre-existing epileptogenic lesion that was 'exposed' by the high fever, or whether the prolonged complex febrile seizure was, in itself, the cause of the subsequent epilepsy. An ongoing study, FEBSTAT [12], is currently under way to image such children soon after their first seizures and then follow them for several years to investigate the possible underlying pathophysiological nature of the problem.

Individuals undergoing craniotomies for any reason are at risk for developing epilepsy. Although it is difficult to separate the risk of seizures caused by a neurosurgical procedure from the risk associated with the reason for the procedure, over 20% of adults develop unprovoked seizures within 2 years of a supratentorial craniotomy. Several antiepileptogenesis clinical trials have been conducted in this situation [13–17]. Most have had relatively small numbers of cases with specific indications for surgery, but the seizure rates in these subgroups give an indication of subgroups with particularly high or low risk, e.g. over 35% chance of unprovoked seizures in those with surgery for arteriovenous malformation, aneurysm in the middle cerebral artery circulation or brain metastases. Scheduled supratentorial neurosurgery provides an unusual opportunity for testing agents that may prevent epilepsy. As was done by Shaw and colleagues [15,17,18], the study treatment can be started prior to scheduled surgery so drug concentrations are already at desired levels before the surgery begins.

Another category of 'brain injury' that is often neglected when discussing risk factors and possible epilepsy prevention is the progressive injuries that occur as a result of chronic neurodegenerative diseases. The incidence of new-onset epilepsy is significantly increased in the population over age 65 [19]. In fact, the incidence in the ageing group is even higher than in young children. The aetiology of epilepsy in this cohort is not completely understood, but cerebrovascular disease, even 'silent', may well be a major cause. However, even after relatively exhaustive examination, in about half the cases, no clear aetiology can be identified. It is well established that individuals with Alzheimer's disease have a higher incidence of epilepsy than their age-matched peers [20,21]. The more clearly identified seizures tend to occur relatively later in the course of the disease, although in familial Alzheimer's disease cases, seizures may present much earlier. Interestingly, Alzheimer's disease patients, even early in the course of their disease, often show fluctuations in their cognitive functions that are not inconsistent with possible partial seizures. A recent study of transgenic mice with an Alzheimer's disease phenotype produced by the expression of a human amyloid mutation demonstrates that these mice exhibit frequent partial seizures, recorded with electrodes implanted into the brains, with a clinical phenotype consisting only of brief staring spells [22]. Extrapolation of these findings to human patients could suggest that some of the variable cognitive performance exhibited by Alzheimer's disease patients might be the result of unrecognized partial seizures.

The presence of mass lesions in or around the brain is another 'risk factor' for epilepsy. Meningiomas, gliomas, tubers and arteriovenous malformations are often accompanied by partial seizures and, in fact, may present as seizures. Identification of these risk factors before seizures develop often occurs because of other neurological symptoms, and it would be possible to treat these individuals to prevent the later development of seizures if such a treatment were available.

Finally, one needs to recognize that even individuals with primary generalized epilepsy that clearly results from a genetic cause almost always develop their seizures well after birth and, thus, would be candidates for a preventative strategy. It is thought that most of these genetically determined epilepsies are a result of a 'channelopathy', which lowers seizure threshold in an anatomically diffuse manner. However, it is possible that treatment before seizures begin could prevent their onset and subsequent consequences of the seizures themselves.

Although the focus of this chapter will remain on the possible treatment of post-traumatic epilepsy, we will continue to discuss possible prevention strategies for other major epilepsy risks. It is possible, if not likely, that if a strategy would work in one form of acquired epilepsy, it might be useful in others as well.

When discussing risk factors for epilepsy, the individual's age and genetic background must be considered as major modifying variables. The consequences of seizures, or brain injuries, in very young children are often significantly different than in older children or adults. For example, bacterial meningitis in young children may result in hippocampal damage, whereas similar infections in older individuals may produce predominantly neocortical damage. In the experimental animal literature, the effects of status epilepticus on very young subjects are often very different than the effects in adult animals, with the young brains being much more resistant to structural damage. Similarly, even febrile seizures in very young animals may have different consequences from similar seizures in older animals. The absence of overt structural damage, however, does not mean the absence of significant neurological deficits, as the young animals may show increased vulnerability to later stresses than their peers. Thus, even when 'damage' is not apparent from an early 'insult', prophylactic measures may be warranted to prevent subsequent epilepsy.

Animal models of epileptogenesis and antiepileptogenesis

Status epilepticus

The most commonly used brain 'insult' to study chronic epileptogenesis has been experimentally induced status epilepticus. Administration of drugs such as pilocarpine or kainic acid will produce focal and generalized seizures in essentially every mammalian species sampled. Similarly, prolonged repetitive brain stimulation can also induce self-sustaining status epilepticus. The status produces widespread damage to neocortex, hippocampus, parahippocampal structures and multiple other areas of forebrain. Depending on the species and strain used, most animals will develop spontaneous seizures within days or weeks of the status. This situation is analogous to human patients who develop chronic epilepsy after an episode of prolonged status epilepticus. Many changes have been identified in the status-injured brain, but the exact mechanisms by which any of these alterations in anatomy, physiology and gene expression produces the chronic epileptic state remain unknown. Numerous attempts have been made to prevent the epileptogenesis in this model but none have succeeded completely. If the convulsive status is blocked by pretreatment of the animals, brain damage can be eliminated and epilepsy does not develop. The degree of damage is dependent on the duration of the status, and administration of drugs that abort the status relatively quickly, such as phenobarbital or other anaesthetics, can reduce the damage and either delay or eliminate the chronic epilepsy. No treatments administered after the status is over have been successful in preventing epilepsy [23,24], although it may be possible to lessen the severity [25]. A variety of AEDs have been tested in this paradigm without success [24].

Kindling

Another commonly used model of epileptogenesis is kindling. Repeated electrical stimulation of the brain with brief trains of stimuli which are not strong enough to evoke seizures but which do evoke afterdischarges (i.e. synchronous EEG spikes lasting beyond the period of stimulation) are applied to a specific area of the brain (e.g. amygdala, hippocampus). Over time, the afterdischarges increase in duration, then begin to spread to other brain regions, and eventually result in generalized seizures. If the process is continued, the animals will eventually develop chronic epilepsy. This form of epilepsy induction results in much less damage to the brain, but is manifest by a variety of changes in local circuits and gene expression. The exact cause of the epilepsy remains unknown, however. Numerous attempts have been made to block the kindling process with AEDs and other medications. In general, if the afterdischarges can be blocked, the kindling process may be blocked. Among the drugs tested, phenobarbital, topiramate and levetiracetam have shown some activity in blocking the kindling process [23,26].

Traumatic brain injury

To date, most experimental studies of TBI have focused on minimizing the damage from the TBI or enhancing a functional recovery. More recent work in a few laboratories has focused on the process of epileptogenesis after brain injury [27]. Injury to neocortex with a controlled lateral percussion has been shown to result in secondary injury to limbic structures, including hippocampus, and has also been linked to increased excitability in hippocampus [28]. More recent work has demonstrated that after some forms of experimental TBI, focal seizures develop around the area of injury. Over time (days to weeks), these seizures can become larger, spread to nearby and distant areas of cortex and become more behaviourally apparent [29,30]. Few data are available about the possible prevention of these seizures after the TBI.

Other forms of 'injury'

For many years, it has been known that if cortex is injured by undercutting its white matter, it becomes hyperexcitable. A number of changes have been identified in these regions that may contribute to the hyperexcitability. Recently, it has been demonstrated that if the undercut cortex is treated with drugs that block action potentials for a critical period after the lesion, the hyperexcitability does not develop [31,32]. Translating these findings into treatments that might be applicable to larger injured area of brain is currently being pursued.

Dysplasias and tumours

As mentioned above, structural lesions in cortex can be very epileptogenic and may be identified before the epilepsy develops. In a transgenic model of tuberous sclerosis, the administration of rapamycin, a drug that acts specifically on the molecular pathway involved in TS, can prevent the development of cortical tubers and can also prevent the development of epilepsy [33].

Primary genetic epilepsy

Many rodent models of primary generalized epilepsy are known. In general, the seizures in these animals respond to many of the same agents that are used to treat similar seizures in humans. Recently, it has been demonstrated that treatment prior to the development of either the EEG trait (spike-and-wave discharges) or the seizures in one form of primary genetic epilepsy results in the prevention of both, as well as the prevention of other, downstream, molecular changes that occur as a consequence of the seizures [34]. These experimental results, along with those from the undercut cortex and TS mouse cited above, can be interpreted as 'proof of principle' experiments demonstrating that epilepsy prevention may be both possible and feasible.

Biomarkers for epileptogenesis

For both experimental studies and human clinical trials, biomarkers that track with the process of epileptogenesis would be extremely useful. Currently, a number of laboratories are investigating biomarkers in TBI, but these are focused on determining the presence and extent of damage to the CNS rather than on the process of epileptogenesis. The main emphasis on biomarkers for epileptogenesis is focused on electrophysiological and imaging biomarkers. Animal data suggest that the presence of EEG spikes, and possibly high-frequency oscillations, may accompany the process of epileptogenesis, and be present before the seizures [35,36]. In human patients, very few data exist on this point. Similarly, researchers are trying to identify specific magnetic resonance imaging (MRI) changes that may accompany

epileptogenesis, specifically hippocampal atrophy and circuit alterations [37].

Is neuroprotection equal to antiepileptogenesis?

As mentioned above, if one can prevent the damage from a brain injury such as occurs after status epilepticus, one can often prevent the subsequent appearance of epilepsy. What is less clear, however, is the extent that partial protection of the brain will also lower the incidence or severity of epilepsy. There are some experimental data that support both sides of this conclusion, but it seems clear that only partial protection is not sufficient to block epileptogenesis reliably.

Human studies of antiepileptogenesis

Over 40 clinical trials have been conducted with a goal of preventing seizures or epilepsy. Almost all have evaluated drugs that are used to treat epilepsy or to suppress seizures. A meta-analysis of the trials with different drugs and different risk factors has been performed [38]. It is helpful to consider trials for provoked seizures separately from those for unprovoked or epileptic seizures. It is also helpful to differentiate treatments that suppress seizures from those that alter the process that causes the brain to generate seizures. Most drug treatments for established epilepsy are of the former variety. When they are at a sufficient concentration, seizures are reduced or eliminated. When the drug is stopped, the seizures return without apparent alteration to the underlying process. Antiepileptogenic treatments, on the other hand, alter the process so that seizures do not occur (or their onset is delayed), even when no seizure-suppressing treatment is present.

Provoked seizures

Provoked seizures occur during or soon after an acute insult. Febrile seizures are the most common provoked seizures. Alcohol-related seizures, contrast media-associated seizures, seizures due to metabolic derangements or infections, and seizures soon after an insult such as a TBI, stroke, aneurysm rupture, or craniotomy are other examples of provoked seizures. In the latter cases, there is no clear demarcation when the 'provocation' ends. Most authors have considered seizures within a week of the insult to be provoked and ones which occur later to be unprovoked or epileptic. The former are often called 'early seizures' and the latter are called 'late seizures'. In virtually every trial to prevent provoked seizures, the therapy tested is itself one that can suppress seizures and it is continued during the period of evaluation. Thus, these trials cannot separate a seizure-suppressive treatment from one which is antiepileptogenic.

The results of meta-analyses of these trials are presented in Figure 19.1. Fourteen trials evaluated five treatments to prevent febrile seizures in children at high risk. Continuous phenobarbital decreased the number of children with additional febrile seizures by about half. Continuous valproate and diazepam, given when a fever is noticed, have results that are promising but unproven, with an effect that is not significantly decreased from that with placebo but with an estimated decrease of at least 25%. Phenobarbital given during a fever or continuous phenytoin had less encouraging results. Phenytoin decreased early seizures after TBI by about two-thirds and carbamazepine decreased them by about 60%. Phenobarbital and the combination of phenobarbital and phenytoin was promising but unproven. Phenytoin similarly decreased early seizures significantly after supratentorial craniotomy and carbamazepine was promising but unproven. Phenobarbital decreased seizures associated with acute cerebral malaria by about two-thirds, and looks promising but unproven for perinatal asphyxia, early seizures after TBI, and early seizures after surgery for brain tumours. Diazepam reduced contrast media-associated seizures by about 90%. Lorazepam decreased alcohol-related seizures by a similar amount, while valproate and phenytoin are promising but unproven for alcohol-related seizures.

All of the above results are based on only clinically reported seizures. Continuous EEG monitoring during the first week after seizures indicates that subclinical seizures are very common and may not be suppressed by standard administration of phenytoin [39,40].

Prevention of epileptic seizures

Traumatic brain injury

Late seizures after TBI have been best studied for the prevention of unprovoked seizures. The initial study conducted by one of the authors (Temkin) at the University of Washington is illustrative of the designs used for the TBI trials [41]. For that study, people whose injury presented at least a 20% risk of unprovoked seizures were randomized to active treatment or identical-appearing placebo and loaded with study drug within 24 h of injury. The initial dose was chosen to produce concentrations within the therapeutic range for treatment of epilepsy. Drug concentrations were monitored at least three times per week in the intensive care unit (ICU), weekly in acute care, and at scheduled visits, and the dose adjusted to keep concentrations within the therapeutic range for the active drug and to maintain masking of placebo. Lorazepam was allowed to treat early seizures, but the participants were supposed to remain on their assigned treatments until either their first unprovoked seizure or one year after injury. Subjects were followed until 2 years after injury so that a seizure-suppressive effect could be separated from an antiepileptogenic effect. Results of the study were that phenytoin reduced early clinical seizures as reported above, but unprovoked seizures were not reduced at all, even during the period of treatment. A total of 27.5% of participants assigned to phenytoin and 21.1% of those assigned to placebo had at least one unprovoked seizure by 2 years. Because not even a suppressive effect was seen, the planned analysis looking for an antiepileptogenic effect (comparing time to first seizure with 18 months after injury) was not reported. A second study at the University of Washington evaluated valproate [42]. The design was similar, but participants in the control arm received 1 week of phenytoin followed by placebo to 6 months after injury. Those assigned to valproate received active drug for either 1 or 6 months and then placebo until 6 months after injury. The results were again disappointing, with a non-significant increase in the late seizure rate with valproate.

The results of the meta-analyses are no more encouraging (see Fig. 19.1). The University of Washington study is the only one to evaluate valproate. Overall, phenytoin was associated with a

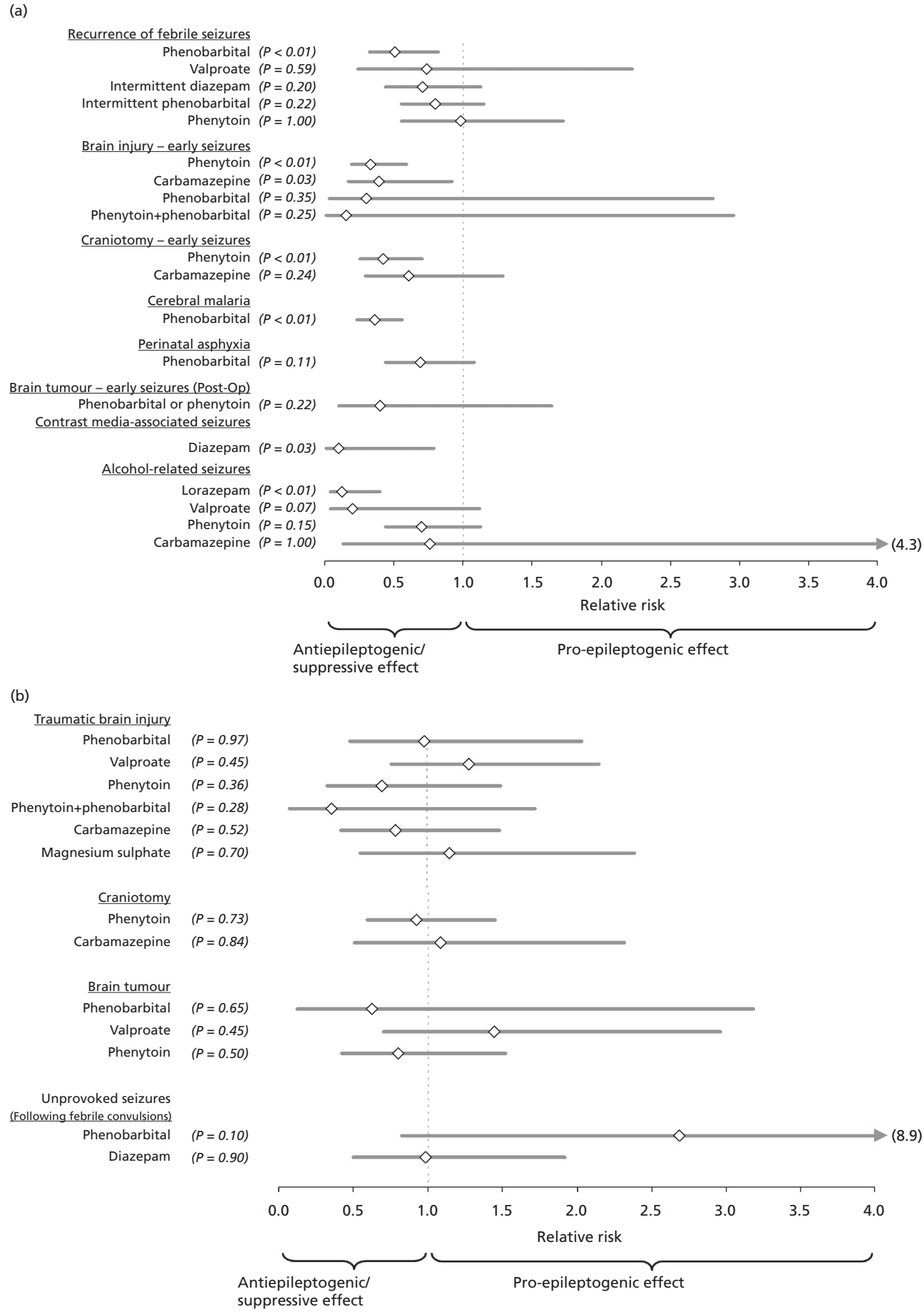

Fig. 19.1 (a) Meta-analyses of studies to prevent provoked seizures. For each condition and drug, the diamond marks the overall relative risk estimate from all studies combined. The line extends to the ends of the 95% confidence interval. A relative risk of 1, representing no treatment effect, is marked by the dashed vertical line. (b) Meta-analyses of studies to prevent epileptic seizures. Results are presented as in part (a). Adapted from ref. 38, with permission.

promising but unproven 30% reduction in late seizures after TBI, but this is driven by a single study with methodological problems (no masking, no placebo and treatment assigned depending on the date rather than by randomization). If only randomized studies are included, phenytoin was associated with a non-significant, 8% *increase* in the number of cases with unprovoked seizures, and the randomized studies in aggregate are compatible with no more than a 24% decrease in the fraction of cases with late seizures. Neither phenobarbital alone nor carbamazepine look promising. The combination of phenobarbital and phenytoin, while having a reduction of two-thirds in the rate of unprovoked seizures, is based on a single study that was stopped early, so even such a large reduction is far from statistically significant ($P > 0.25$). The single study of a drug not generally considered to suppress seizures evaluated magnesium sulphate beginning within 8 h of injury and continuing for 5 days by continuous infusion. Neither early nor late seizures were reduced [43].

Craniotomy

Studies of late seizures after craniotomy are equally disappointing. Neither phenytoin nor carbamazepine shows anywhere near a significantly positive effect, even though the treatment was begun several days before the surgery.

Brain tumours

In studies attempting to prevent seizures in patients with brain tumours, valproate and phenytoin did not look promising, while the 40% reduction with phenobarbital was from a study that was so small that even that reduction was not close to statistical significance ($P = 0.65$).

Febrile seizures

Several studies evaluating diazepam and continuous and intermittent phenobarbital for prevention of febrile seizures followed their cases for years after treatment stopped to see if the treatment affected epileptogenesis. The number of unprovoked seizures was small and there was no suggestion of an antiepileptogenic effect.

Febrile status epilepticus

Children with prolonged and/or complicated seizures associated with fever are at high risk for developing chronic epilepsy. The exact risk is unknown, as is the question of whether such children had a prior neurological abnormality which was exacerbated by the febrile illness and was the true underlying basis for the episode of status. Recently, a co-operative epidemiological study (FEBSTAT) was developed to study children with new-onset status epilepticus associated with fever, but without other obvious cause, to determine the nature of the brain injury sustained by these children, their true risk for developing chronic epilepsy, and to attempt to identify possible biomarkers associated with the development of epilepsy after febrile status [12]. One long-term goal of this study is to try to intervene in those children at high risk so as to prevent the development of epilepsy.

Dysplasias

Although the focus of this chapter is on the prevention of epilepsy after injuries to the brain, it is worth briefly considering other epilepsy prophylaxis studies as well. Individuals with tuberous sclerosis, especially those with intracranial tubers, are at very high risk for developing epilepsy. These individuals can often be identified by family history. Recent laboratory experiments have demonstrated that transgenic mice with the *TS1* mutation will also develop seizures and that the seizures can be prevented by treatment with rapamycin [33]. Unfortunately, the mice require permanent treatment to prevent the seizures. If treatment is stopped the seizures may start. Recently, a pilot clinical trial was initiated to treat children with this mutation with rapamycin to try to prevent epilepsy. Long-term efficacy and safety will need to be carefully established before such treatment becomes acceptable in human patients. However, if this trial is successful, it will be the first demonstration of a prophylactic treatment preventing or even postponing epilepsy in humans.

Limitations of the clinical trials performed to date

The trials performed to date, while disappointing with respect to affecting epileptogenesis, cannot rule out the possibility that these drugs might have an effect. Most studies were small, and even combining their results through meta-analysis cannot rule out a modest effect in all cases and even a substantial effect in many. The doses used were based on what is usual for treating epilepsy and may not be the correct dose for affecting epileptogenesis. Even in the case of early seizures, in which several drugs suppressed clinical seizures, we do not generally know if electrical seizures were also suppressed. Most studies could begin treatment out to 24 h after the insult and that might be too long to affect the process, although the study of planned craniotomy that started treatment prior to surgery showed no more encouraging results. After participants were discharged from the hospital, studies could not ensure compliance. The University of Washington studies measured serum concentrations at scheduled visits and they generally reflected the level of compliance reported by the participants, but that does not ensure that the drugs were taken as consistently between visits. The closest to random serum concentrations were obtained when a participant came into the emergency department because of a seizure. Of the nine patients in whom this occurred, seven had concentrations in the desired range.

Studies that have been carried out have not been based on extensive preclinical work. Although it seems reasonable that a drug that suppresses seizures might prevent them from developing, this has not been demonstrated for any of the AEDs evaluated to date. Dose, critical time window and necessary duration have also not been evaluated in preclinical models. Magnesium was evaluated based on its general neuroprotective effect in the laboratory and its ability to prevent seizures in women with pre-eclampsia, not on a demonstrated antiepileptogenic effect in the laboratory. With the recent development of post-traumatic seizure models, one might expect more knowledge about what is happening in the clinically silent period between the injury and the clinical expression of seizures. This in turn could allow treatments that target specific parts of the process and might truly be antiepileptogenic. If the effects are borne out in clinical trials, these could provide the treatments for those with RED syndrome.

Treatment of post-traumatic epilepsy

Pharmacological treatment of seizures

Seizures developing after TBI are localization-related partial seizures and are treated the same as partial seizures, without, or with, secondary generalization, due to any other cause. There is no evidence that any of the AEDs that are effective in treating partial seizures are more or less effective for post-traumatic epilepsy (PTE). However, there are some special issues that should be considered when choosing among the many available AEDs. Patients with TBI often have problems beyond their seizures, including cognitive, motor and psychological problems resulting from the TBI. These factors must be considered when choosing a first AED. For example, if an AED that may have cognitive side-effects, such as topiramate, is chosen, it is important to carefully monitor the patient for additional cognitive difficulties that could be related to the drug as opposed to the brain injury. Similarly, with medications that may have behavioural side-effects, such as levetiracetam, zonisamide or phenobarbital, careful monitoring of the patient's behaviour after addition of the drug needs attention. In addition, individuals with moderate to severe brain injury may have a compromised level of consciousness; thus, sedating medications should be avoided. In general, all available AEDs have potential side-effects, even if in a small minority of patients, and these may be exacerbated in an individual with significant pre-existing morbidity due to the TBI.

Of particular concern in this group of patients is the issue of non-convulsive seizures. Individuals with TBI may have cognitive and behavioural changes due to the TBI. In addition, however, if such individuals develop non-convulsive partial seizures, the major clinical manifestations of which are periodic decreases in cognitive function or periodic behaviour changes, these seizures may not be recognized and will go untreated. This is particularly problematic in this patient population because these unrecognized seizures can add significantly to the patient's disabilities while being potentially treatable. Even physicians might not recognize the symptoms as being caused by non-convulsive complex partial seizures. What makes this issue even more difficult is that the background EEG may be abnormal but this is attributed to the effects of the TBI itself and even prolonged EEGs may not demonstrate the seizures if they are occurring deep in the brain and are not conducted to the surface of the neocortex. Comprehensive epilepsy centres with large presurgical evaluation programmes commonly see patients whose seizures are only noted on depth electrodes and are not detected in scalp recordings. When such non-convulsive seizures are suspected, a short trial of antiepileptic medication may be the only way to make a correct diagnosis and help the patient. Moreover, increased education of patients, family members, other care providers and all of the medical professionals who deal with TBI patients should be developed to ensure that such paroxysmal changes in cognitive function or behaviour are recognized as potential complex partial seizures.

Surgical treatment of intractable seizures after traumatic brain injury

Individuals with uncontrollable partial seizures may be candidates for ablative surgery for seizure control. Those with a well-localized seizure focus that exists in an area of brain that can be safely removed are the best candidates for epilepsy surgery. This may apply specifically to individuals that sustain unilateral temporal lobe damage, either directly or secondary to the hypoxia and hypotension that may accompany severe trauma. Unfortunately, most individuals with moderate to severe TBI who develop PTE have multifocal brain lesions, many of which could be epileptogenic. It is possible that careful studies will be able to localize the source of the seizures to a region that can be removed safely, but, in general, this is likely to be much more difficult than localization of seizure foci from other causes. In addition, the presence of extensive, multifocal brain injuries will make it more difficult to determine whether removal of any specific epileptogenic region can be performed without leaving the patient with additional deficits. Thus, although epilepsy surgery is sometimes a viable option for achieving seizure control after TBI, it requires a careful case-by-case evaluation and a recognition of the complications inherent in this group of patients.

Recommendations

Currently, administration of phenytoin for 1 week is recommended for treatment after TBI to suppress early clinical seizures. There is good evidence, however, that phenytoin does not reduce the risk of subsequent chronic epilepsy. Despite this, many neurologists and neurosurgeons maintain their patients on phenytoin. More recently, there has been a tendency to utilize several of the newer AEDs for prophylaxis, especially levetiracetam because of its ease of use, but there are no data to indicate that levetiracetam is as efficacious as phenytoin for preventing early seizures, nor if it is useful for preventing chronic epilepsy. It is clear that more well-designed clinical trials are needed to establish whether newer AEDs are as effective, or more effective, in preventing early seizures. Study of levetiracetam after TBI is currently in the pilot/planning phase. Because phenytoin may be more effective in suppressing clinical seizures than electrographic seizures, these studies need to be carried out with long-term EEG monitoring, at least during the first week after TBI. It must also be mentioned that there is suggestive evidence that treatment with some AEDs after stroke or TBI may retard recovery from the injury [44,45]. This was not seen in the controlled trials of phenytoin after TBI, however [46]. Future studies of epilepsy prevention need to consider this when examining outcomes.

Experimental animal research suggests that small localized seizures may occur early after TBI and that these seizures may not be seen with scalp recordings. It is not clear if suppression of such seizures would lead to an antiepileptogenic outcome, but this is a reasonable hypothesis. In addition, other experimental studies have suggested that the early appearance of interictal spike discharges, or high-frequency oscillations, may also act as biomarkers of the process of epileptogenesis. Each of these phenomena would be much more likely to be identified with chronic EEG recording from intracranial electrodes. Currently, such recordings are not a part of our clinical repertoire, but it is possible that in the future it will be desirable to consider such recordings, if they can be accomplished in a safe and minimally invasive manner, as part of a routine seizure prophylaxis protocol.

Similarly, although we can identify potentially epileptogenic lesions by brain imaging, the development of specific imaging biomarkers for the process of epileptogenesis after TBI or other brain insults has not yet been established. This is another area in which non-invasive investigations may allow us to identify those at highest risk and tailor new therapies accordingly.

As the process of epileptogenesis, whether after TBI or any other injurious process, is better understood from a mechanistic perspective, it is hoped that specific therapies can be directed against the critical processes to prevent the development of chronic epilepsy. Such new therapies may be quite different from conventional antiseizure therapies and could, for example, involve temporary interference with specific gene expression patterns that occur after injury. This is the dream of much of current epilepsy research. However, even if such strategies can be developed in the laboratory, it will still require careful clinical protocols, with relatively long-term follow-ups, to demonstrate their effectiveness and safety in human patients. Designing such clinical trials and establishing the infrastructure for their implementation is one of the major challenges in contemporary clinical investigation in epilepsy.

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20 Management of Medical Co-morbidity Associated with Epilepsy

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Introduction

Co-morbidity is a term that refers to the occurrence of one or more additional disease(s) in an individual with an index disease (herein, epilepsy) [1]. Although not necessarily the case, the index and co-morbid disorder(s) may have some bearing on the incidence, course and treatment of the other. Physicians involved in specialized epilepsy care frequently encounter co-morbidity. The association between epilepsy and several psychiatric disorders is well known and is an example of co-morbidity (this topic is reviewed in Chapter 21 and is not considered further here). Multimorbidity, on the other hand, is a term referring to the concurrent occurrence of several chronic disorders generally requiring treatment in an individual, commonly used in the context of general practice. The occurrence of seizures requiring treatment in an elderly individual with cardiac disease, prostatism, and mild age-related renal impairment is an example of multimorbidity. Physicians involved in specialist epilepsy practice frequently encounter co-morbidity, while primary care physicians involved in epilepsy care in the community have to deal with multimorbidity, epilepsy being one of the many components. Both co-morbidity and multimorbidity are commonly encountered in the treatment of epilepsy. However, in comparison with psychiatric disorders, the medical (or somatic) co-morbidity of epilepsy is less well appreciated. From the epidemiological standpoint, an increased mortality due to cardiovascular disorders, pulmonary disorders as well as certain cancers has been noted in people with epilepsy [2,3]. Limited data also exist on the incidence and nature of somatic disorders experienced by people with epilepsy during their lifetime. These data suggest that the prevalence rates of cardiovascular disorders, infections, pulmonary disease and gastrointestinal haemorrhage are increased in this population [4]. Reviewed here are aspects of the medical co-morbidity of epilepsy that are important from the clinical standpoint. Several disorders are considered, including hepatic and renal impairment, infectious disorders, connective tissue diseases and pulmonary and cardiac disorders.

Relevant to the co-morbidity of these disorders with epilepsy is the modification of the treatment of the latter imposed by these medical conditions. Furthermore, several medical disorders may arise during the course of epilepsy as a consequence of its treatment (e.g. disorders of bone). The prevention, recognition and treatment of these disorders are an integral component of comprehensive epilepsy care.

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Bone health in epilepsy

Although the effects of epilepsy and its treatment on bone structure and function have been investigated for many years, the clinical implications of this interaction have been appreciated only very recently. Two skeletal disorders (i.e. osteomalacia and osteoporosis) are noteworthy in consideration of the impact of epilepsy and antiepileptic drugs (AEDs) on bone health. Osteomalacia is a disorder in which mineralization of the bone is selectively impaired, most often due to deficiency of vitamin D, and osteoporosis refers to generalized loss of bone mass with profound decline in microarchitectural organization leading to a propensity to bone fractures. Although the two disorders do not directly fall within the scope of epileptological practice, a growing recognition of the frequency of occurrence of both osteomalacia and osteoporosis in people with epilepsy demand of the epileptologist the necessary skills to be able to screen and counsel about bone health.

Overview of bone physiology and biochemistry

The bone comprises mineral made up for the most part by calcium and collagenous matrix. Predictably, therefore, disorders of calcium homeostasis affect bone structure and function. The metabolism of calcium in the human body is rather complex and is regulated by two hormonal factors: vitamin D and parathyroid hormone (Fig. 20.1). Vitamin D is acquired from diet and through the skin as a result of sunlight exposure. Accordingly, exposure to sunlight and dietary items such as cereals and fish oils are the principal sources of body stores of this vitamin. In the human body, vitamin precursors acquired through skin and diet are first hydroxylated in the liver to 25-hydroxyvitamin D_3, which is the measurable fraction of the vitamin in plasma. The 25-hydroxyvitamin D_3 is subsequently hydroxylated again in the kidney. The final product, 1,25-dihydroxyvitamin D_3, is the active form of the vitamin as it mediates absorption of calcium in the gut and mobilization of calcium from the bone in addition to exerting a negative feedback control over the secretion of parathyroid hormone by the parathyroid glands. The parathyroid hormone itself induces the mobilization of calcium from the bone.

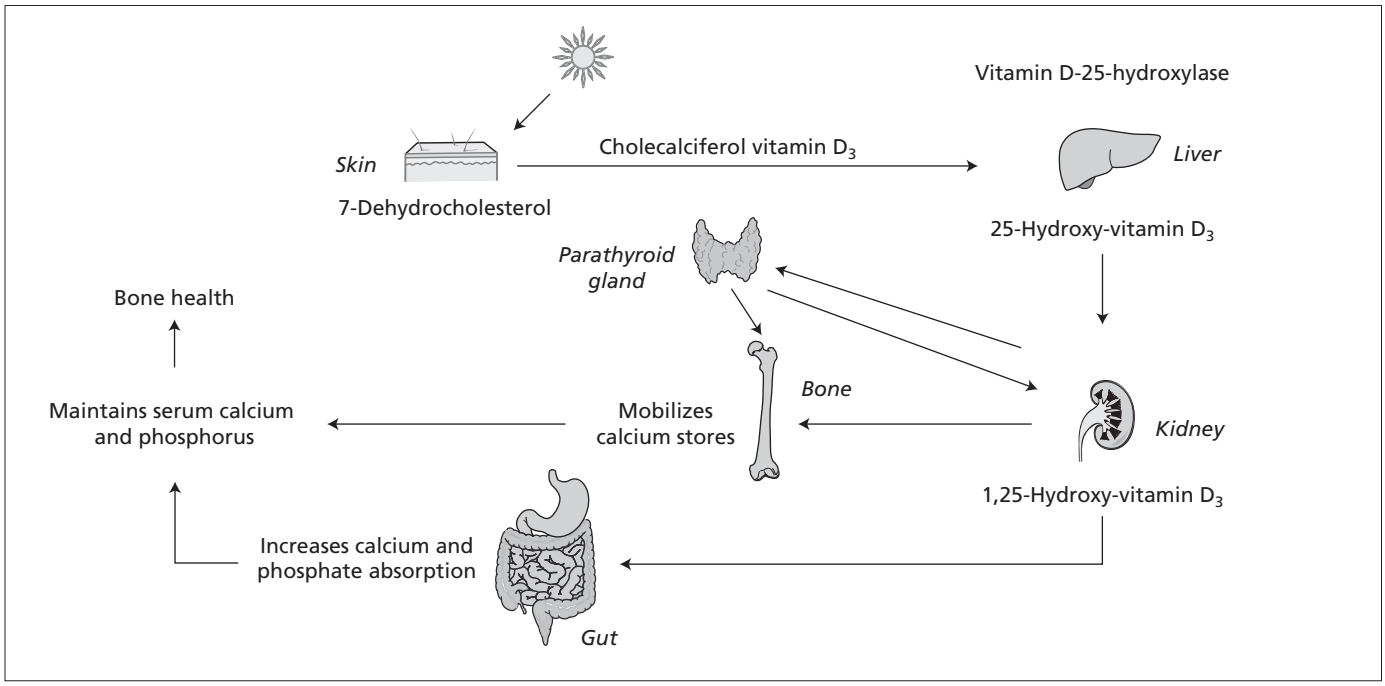

Fig. 20.1 Calcium metabolism pathways in the human body.

Across the span of the human life cycle, there is a period of intense accrual of bone mineral up to the age of 20–30 years, followed thereafter by first a plateau phase and then a gradual decline in bone mineral density. In women, bone loss increases in the postmenopausal period owing to oestrogen deficiency. At any given age, bone mineral density is a function of the peak bone mass accrued in the early period of life and the rate of bone loss. Peak bone mass is determined primarily by genetic factors but also by environmental variables such as nutritional intake and physical exercise (specifically, weight-bearing exercise). On the other hand, bone loss is the result of oestrogen deficiency in the postmenopausal period (in women) and is influenced by physical activity and, to a small extent, by contemporaneous calcium and vitamin D intake. Also influential in this context are several medications (e.g. glucocorticoids and AEDs), alcohol and cigarette smoking, all of which hasten the process of bone loss. The end result is a progressive reduction in bone strength and eventually frailty (or non-traumatic) fractures. The hip, vertebral bodies and wrist are the common sites of frailty fractures. The consequences of such fractures (frailty fractures) include increased mortality and long-term morbidity (due to chronic back pain and immobility), and these fractures pose a social and tremendous economic burden.

Fracture and osteoporosis risk in people with epilepsy

The risk of developing any fracture is two to three times higher in people with epilepsy than in the general population [5]. Of all fracture sites, the risk appears maximally elevated for the hip and vertebral bodies. Fractures in people with epilepsy may be related to the strain experienced by bones during generalized tonic–clonic seizures, falls during generalized seizures and accidents during generalized and complex partial seizures. An increased risk of frailty fractures has also been reported and can be attributed to reduced bone mineral density in people with epilepsy (Table 20.1) [6]. In some early studies, insufficient ambulation directly due to epilepsy and its associated neurological handicaps, poor nutritional status and inadequate exposure to sunlight (leading to vitamin D deficiency) in institutionalized people with epilepsy were cited as reasons for reduced bone strength. However, bone mineral deficits have also been documented in ambulatory as well as outpatient populations of epilepsy, and it is now thought that AED therapy is an important factor in the development of bone mineral deficits [7,8]. The most consistent adverse effects on bone metabolism have been found with the enzyme-inducing AEDs (phenytoin, phenobarbital and primidone). Evidence of impaired bone metabolism with carbamazepine is somewhat conflicting [9,10; reviewed in ref. 11]. Valproic acid treatment is also associated with reduced bone mineral density and this effect appears to be independent of vitamin D-related mechanisms [9,12]. The effects on bone metabolism of the newer AEDs have not been extensively studied but preliminary data do not reveal any consistent effect on various parameters of bone health [13–15].

Compromised bone health not only occurs in adults but has also been documented in children with epilepsy, in whom a poor accrual rather than accelerated loss of bone mineral is believed to be responsible for inadequate bone mass [11,16,17]. Poor bone accrual in childhood may lead to rickets or osteomalacia or simply to inadequate height and growth progress. Moreover, reduced peak bone mass due to poor accrual in

Table 20.1 Putative factors and mechanisms associated with increased fracture risk in people with epilepsy.

Seizure-associated fractures
Bone strain during generalized tonic–clonic seizures
Fractures during falls associated with generalized seizures or AED toxicity
Fractures associated with accidents during generalized and complex partial seizures
Frailty fractures associated with reduced bone mineral density
Increased metabolism of vitamin D in liver by enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbital, primidone and, to some extent, topiramate and oxcarbazepine
Direct toxic effect on bone (phenytoin-sodium)
Increased bone resorption (valproic acid)
Impaired gut absorption of calcium (due to vitamin D deficiency and direct effect of phenytoin)
Increased catabolism of oestrogens due to enzyme-inducing AEDs
Vitamin K deficiency in users of enzyme-inducing AEDs
Renal tubular dysfunction associated with valproic acid use
Elevated homocysteine levels leading to poor bone collagen formation
Deficient vitamin B_{12} and folate levels leading to poor bone collagen synthesis
Up-regulation of 24,25-hydroxylase in renal tissue, promoting the conversion of 1,25-dihydroxy-vitamin D_3 to inactive compounds by phenobarbital, phenytoin and carbamazepine
Sedentary lifestyle of people with epilepsy predisposing to osteoporosis
Poor sunlight exposure in institutionalized people with epilepsy leading to vitamin D deficiency
Poor nutritional status of people with epilepsy leading to vitamin D deficiency
Altered smoking and alcohol habits in people with epilepsy

AED, antiepileptic drug.
From refs. 5, 6, 9, 12, 20, 147, 148 and 149.

early life increases the risk of developing osteoporosis in later life.

Screening for bone health in people with epilepsy

At present, the dual-energy X-ray absorptiometry (DEXA) scan is the most widely used and reasonably reliable screening method for assessment of bone health. The test measures bone mineral density at selected sites and for the purpose of analysis compares the index bone density to the peak bone density of a young adult of the same gender to generate a T-score. A T-score >1 standard deviation (SD) below the comparator signifies osteopenia and >2.5 SD suggests osteoporosis. The DEXA scan is indicated routinely in postmenopausal women, those with premature ovarian failure, hyper- or hypoparathyroidism, those requiring long-term (>3 months) glucocorticoid treatment and those with radiological evidence of osteoporosis in the vertebrae and prior frailty fracture [18]. There are no standard recommendations regarding the estimation of bone mineral density in people with epilepsy. Some authors recommend that a DEXA scan be undertaken in all people with epilepsy of greater than 2–5 years' duration, those who are receiving enzyme-inducing AEDs, those with symptomatic epilepsy and those commencing treatment in the postmenopausal period [19,20]. The UK National Institute for Health and Clinical Excellence (NICE) recommends estimation of serum calcium, phosphorus, alkaline phosphatase and 25-hydroxyvitamin D_3 every 2–5 years in those adults with epilepsy on enzyme-inducing AEDs. In addition, people with epilepsy should be screened for additional risk factors for osteoporosis as the presence of these may compound the risk of osteoporosis and frailty fractures. The risk factors include age >65 years, postmenopausal status in women, prior frailty fracture, corticosteroid therapy, low body weight and thyroid, parathyroid and gonadal disorders. Screening procedures for bone health in children with epilepsy are uncertain.

Prevention and treatment of bone loss in people with epilepsy

Several aspects of prevention and treatment should be considered in optimizing bone health status of people with epilepsy. Adherence to weight-bearing exercise protocols and avoidance of cigarette smoking and excessive alcohol intake are general measures that need to be followed. Recommendations for supplementary intake of calcium and vitamin D should be based on calculation of daily dietary intake of these items. The required intake of calcium is 1200 mg/day and of vitamin D is 800 IU/day. It is not clear if people using enzyme-inducing AEDs require higher doses of vitamin D due to increased catabolism of the vitamin. However, if vitamin D_3 levels remain in the subnormal range despite routine supplementation, higher doses of the vitamin may be used. In those in whom bone mineral density is in the osteoporotic range (i.e. T-score <–2.5 SD), a range of treatment options are available including bisphosphonate agents, strontium and calcitonin. The advice of an endocrinologist should be sought in such situations. In all people with epilepsy in whom bone mineral density is in the impaired range, a review of medications in order to choose an AED that does not adversely impact bone health should be considered.

Organ impairment

Seizures and epilepsy can occur concomitantly with organ (e.g. hepatic, renal or endocrine) dysfunction and may or may not be related to the latter. At times, the organ impairment may involve multiple systems (multiorgan dysfunction). The presence of concomitant organ failure in epilepsy has the following implications in the management of epilepsy:

1 Seizures may occur due to organ (e.g. renal) dysfunction or as a manifestation of a disorder that affects the brain as well as the body organ.

2 Organ impairment may have an effect on the treatment of seizures and epilepsy.

3 Organ dysfunction may occur as a complication of epilepsy or its treatment.

4 The occurrence of epilepsy may impact the treatment of the organ disorder.

The first of the issues is considered elsewhere, and the remaining three are reviewed in subsequent sections of this chapter. Relevant in this context are the altered pharmacokinetics as well as pharmacological responsiveness to medications used in the treatment of both seizures and epilepsy as well as organ dysfunction as a result of drug disease and drug–drug interactions. Drug–drug interactions are described in detail elsewhere in this volume (Chapter 28) and are considered only briefly here.

Overview of AED pharmacokinetics in hepatic and renal disease

Antiepileptic drug metabolism occurs largely in the liver, while AED elimination usually takes place in either the liver or the kidney or both. The liver and kidney are also involved in synthesis and regulation of plasma proteins and many AEDs are extensively protein bound. Hence, both hepatic and renal dysfunctions affect AED pharmacokinetics through a variety of mechanisms.

The determination of AED dosages in liver disease depends upon the estimation of residual hepatic function. However, no single clinical or laboratory parameter can be utilized as a measure of the estimate of available hepatic function. Hence, dosage considerations are based on clinical assessment of the response to AED (i.e. degree of seizure control) and side-effects (chiefly, neurological side-effects, which are dose dependent), supplemented by total and free drug levels whenever available. The Child–Pugh system of grading liver disease may be used to estimate the degree of impairment in chronic liver disease (Table 20.2) [21]. However, there is limited experience with its use in predicting dosages for those newer AEDs for which estimation of serum levels is not an option [22,23].

The liver extracts drugs from the portal circulation following their absorption through the gastrointestinal mucosa. In addition, it is involved in the metabolism and elimination of many drugs and is the site of synthesis of plasma proteins. Hence, on many accounts, it crucially controls the pharmacokinetics of several drugs including both conventional and many of the newer AEDs. An initial step comprises the extraction of the drug from the portal circulation (the first-pass effect). For most AEDs, the hepatic extraction ratio, which is a measure of the first-pass effect, is reasonably low. A further step is drug metabolism and elimination, which is accomplished in the liver through two sets of reactions (for most but not all AEDs metabolized in the liver), known as the phase I and phase II metabolic reactions. The former comprise mainly oxidation reactions and are involved in altering the functional status (from active to inactive or vice versa) of the drug molecule. The phase I reactions are most vulnerable to impaired hepatocyte function. Since oxidative enzymes in the liver are saturable, the metabolism of drugs through these reactions is limited by the hepatic enzymatic capacity (capacity-limited metabolism, e.g. phenytoin). Phase II reactions involve conjugation and are important for drug excretion.

Table 20.2 Child and Pugh's classification of chronic liver disease.

Measure	One score	Two scores	Three scores
Serum total bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (mg/L)	>35	28–35	<28
Prothrombin time (international normalized ratio)	<1.7	1.71–2.20	>2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

Class A, score of 5–6; class B, score of 7–9; class C, score >10.
Source: [21].

The disorders of liver are several, but from the standpoint of AED prescribing may be divided into acute hepatic necrosis (due to toxins and viral hepatitis) and chronic liver disease (i.e. cirrhosis) (Table 20.3). On the basis of the limited data available, it may be inferred that acute liver insults (e.g. viral hepatitis) do not significantly alter the pharmacokinetics of AEDs [24,25]. Dosage adjustments are, however, often required in cirrhosis due mainly to changes in the proportion of the AED metabolized and eliminated in the liver and in the degree of protein binding. As all available AEDs have low hepatic extraction ratios, this is not normally a factor to consider. The conventional AEDs, including phenytoin, valproate, carbamazepine, phenobarbital and primidone, are metabolized chiefly in the liver. Of the newer AEDs, tiagabine and lamotrigine are metabolized almost exclusively in the liver, and oxcarbazepine, felbamate, topiramate, zonisamide and levetiracetam are partially metabolized in the liver and partially excreted unchanged in the urine. Gabapentin and vigabatrin are excreted unchanged by the kidney [26]. The degree of protein binding is high for certain AEDs including phenytoin, valproate, carbamazepine and tiagabine. In many liver disorders, impaired synthesis of albumin and protein binding by excess circulating bilirubin results in a reduced fraction of the protein-bound drug and elevated free levels of the drug. Hence, estimation of free drug levels of some drugs may be preferable in chronic liver disease.

In renal impairment, reduced glomerular filtration and tubular secretion can result in decreased drug elimination. In addition,

Table 20.3 Practical considerations in the management of epilepsy and seizures in hepatic dysfunction.

Institution of long-term AED treatment in individuals with pre-existing chronic liver disease
The use of valproate and felbamate (and possibly carbamazepine, phenytoin and lamotrigine) is to be avoided
The use of gabapentin appears safe
Levetiracetam and topiramate appear safe in mild chronic liver disease but dose reduction must be considered in Child's C hepatic impairment
Use slower titrations and lower maintenance doses if possible
Dosage considerations should be guided by free AED concentrations whenever available
Occurrence of acute hepatic dysfunction in individuals on AED treatment
Ongoing treatment with valproate to be stopped and the agent should be replaced with an alternative AED
Establish if the hepatic failure is related to AED. If related to AED, the drug should be stopped and replaced with an alternative (Note: AED-induced acute hepatic failure is rare in comparison with other causes of acute hepatic failure)
Dosage modification is often not required for AEDs except in severe hepatic failure, in which case it should be guided by clinical response and free-AED concentrations
Acute seizure control in acute hepatic failure (e.g. due to viral hepatitis or alcohol)
The use of benzodiazepines for seizure control is to be avoided. Midazolam may be used if required, in view of its short duration of action
Phenytoin (in loading dose), phenobarbital, gabapentin and levetiracetam may be administered to control repetitive seizures or status epilepticus or to prevent recurrent seizures

AED, antiepileptic drug.

Table 20.4 Dosage adjustments for newer AEDs in patients with reduced kidney function.

AED	Total daily dose (GFR, ml/min)				Estimated loss during haemodialysis	Supplementary dose after haemodialysis
	60–89	30–59	15–29	<15		
Gabapentin	400–600 mg thrice daily	200–300 mg twice daily	200–300 mg/day	100–150 mg/day or 300 mg every other day	NA	125–250 mg
Levetiracetam	500–1000 mg twice daily	250–750 mg twice daily	250–500 mg twice daily	250–500 mg twice daily	50%	250–500 mg
Topiramate	100–200 mg twice daily	50–100 mg twice daily	50–100 mg twice daily	50–100 mg twice daily	50%	50–100 mg
Zonisamide	100–400 mg	100–400 mg	Insufficient data; use with caution		50%	Supplement 50% dose if seizure occurs after haemodialysis
Oxcarbazepine	300–600 mg twice daily	300–600 mg twice daily	50% of original dose	Insufficient data; use with caution	NA	NA
Felbamate	1200–3600 mg	Insufficient data; reduce dose by 50%			NA	NA
Lamotrigine	100–500 mg	Insufficient data; may benefit from decreased dose			NA	NA
Tiagabine	32–56 mg	No dose adjustment necessary			NA	Not required

NA, data not available.
Adapted from ref. 27 with permission.

both quantitative (e.g. protein loss in nephrotic syndrome) and qualitative changes in plasma proteins occur in renal disorders. Uraemic toxins may compete with AEDs in order to bind to plasma proteins, chiefly albumin. The net effect is reduced protein binding and hence increased free drug levels in the plasma. Oral bioavailability of drugs is also compromised as a result of poor gastrointestinal absorption in uraemia. Finally, hepatic metabolism and elimination of AEDs is also altered in uraemia. The overall effect of renal impairment on AED pharmacokinetics is therefore complex and unpredictable. However, in clinical practice, dosage considerations are most often made based on the fraction of the active drug that is eliminated by the kidney (Table 20.4) and functional renal status. Estimation of the functional renal status involves calculation of creatinine clearance from the serum creatinine concentration using the following formula: creatinine clearance = (140 – age in years) × weight in kg/72 × serum creatinine.

Since the apparent volume of distribution of AEDs is presumed to be unaffected in renal impairment, the loading dose of AED when required remains the same as in healthy subjects. Maintenance doses, however, need to be adjusted according to creatinine clearance for AEDs eliminated through the renal route (Table 20.4) by either reducing the dose of the drug dispensed or increasing the time interval between dose administrations. Furthermore, both acute renal failure and end-stage renal disease due to chronic renal failure obligate the use of extracorporeal techniques (haemodialysis, continuous or intermittent peritoneal dialysis, haemofiltration and haemoperfusion) in order to remove uraemic and extraneous toxins, which may also lead to loss of AED from the body. Removal of a drug during dialysis depends on several factors including the molecular weight, degree of protein binding and water solubility of the drug and is hence different for each of the several available AEDs. For certain AEDs, consideration of dialysis-related drug loss entails the administration of supplemental doses in the immediate post-dialysis period (see Table 20.4).

Pharmacokinetic data regarding individual AEDs in renal impairment have been reviewed recently [27] and are summarized in Table 20.4. Dosage guidelines in impaired renal function based on creatinine clearance are available. For those renally excreted AEDs that are targets for the cytochrome P450 (CYP450) enzyme system (e.g. topiramate and felbamate), the proportion of the drug that is metabolized in the liver is increased when enzyme-inducing AEDs are concomitantly administered [28,29]. This effectively decreases plasma concentrations of the target drugs. Hence, dosage adjustments may not be required for these drugs when administered concomitantly with enzyme-inducing AEDs in the setting of renal failure.

Hepatic and renal impairment due to epilepsy and its treatment

Either hepatic or renal impairment may develop during the course of epilepsy or its treatment. There is a considerable body of literature available on hepatic disorders developing during the course and treatment of epilepsy. In comparison, renal impairment is less common [30,31]. Relevant to the finding of hepatic impairment during the course of epilepsy is the concern whether the clinical or laboratory abnormalities indicating hepatic dysfunction are the result of AED toxicity. The finding of otherwise asymptomatic elevation of serum transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], γ-glutamyl transferase (GGT) and alkaline phosphatase (ALP) up to two to three times of the upper limit of normal is common with chronic treatment with enzyme-inducing AEDs including phenytoin, carbamazepine, phenobarbital, primidone, topiramate and oxcarbazepine, owing to induction of hepatic microsomal enzyme systems [32]. This finding does not constitute an indication for further investigation or drug or dose modification but requires that baseline liver function parameters be estimated prior to commencement of treatment with enzyme-inducing AEDs. There appears to be no role for the routine monitoring of liver function tests during treatment with any of the AEDs. The ele-

vated ALP in the plasma during prolonged treatment with phenytoin may be of skeletal rather than hepatic origin [33]. Elevation of arterial or venous blood ammonia levels is frequent in individuals on treatment with valproate and the mild elevation usually encountered is of no clinical significance [34]. Hence, routine monitoring of arterial or venous blood ammonia levels during valproate therapy is generally not recommended. However, if unexplained encephalopathy develops following commencement of valproate therapy, estimation of ammonia levels should be undertaken in consideration of the likelihood of hyperammonaemic encephalopathy.

As a class of drugs, AEDs are the third most common cause of serious drug-induced hypersensitivity reactions affecting the liver in clinical practice [35]. Overall, however, the incidence of hypersensitivity is low. Clinically significant hepatic damage due to hypersensitivity has been commonly reported with valproate, phenytoin, felbamate and probably carbamazepine and lamotrigine, but there are only anecdotal descriptions of liver disease developing due to other AEDs. Hepatic dysfunction due to AEDs is a type B reaction; that is, it is idiosyncratic, unpredictable and not dose related, and occurs in (genetically) susceptible individuals [36]. From the mechanistic standpoint, the idiosyncrasy may be either immunoallergic (e.g. with phenytoin, carbamazepine and lamotrigine) or metabolic (with valproate). Phenytoin-induced hepatic dysfunction typically occurs in the setting of generalized hypersensitivity reactions and hence is accompanied by fever, skin rash, lymphadenopathy, nephritis and peripheral blood eosinophilia [37]. The onset of hepatic dysfunction is within 1–6 weeks of commencement of phenytoin therapy. Hypersensitivity features such as eosinophilia appear to be less common with carbamazepine than with phenytoin [37]. The production of the reactive metabolites' arene oxides has been shown to be critically involved in hepatic reactions to both AEDs. These metabolites are detoxified by the enzyme arene epoxide hydrolase to non-toxic excretory products. In susceptible individuals, however, a deficiency of this enzyme leads to an accumulation of arene oxides, which cause hepatic injury [38]. On the other hand, valproate causes hepatic dysfunction owing to its peculiar metabolic degradation in predisposed individuals (see below). Valproate mainly undergoes glucuronidation (phase II reaction) in the liver. However, 20% of its hepatic metabolism occurs by oxidation (phase I reaction), which takes place both in the mitochondria and in the endoplasmic reticulum [39]. Normally, mitochondrial oxidation (known as beta-oxidation) of valproate dominates over cytosolic oxidation (also known as omega-oxidation) and involves carnitine as a carrier molecule leading to the formation of the metabolic product, 2-en-valproic acid. In predisposed individuals or in the setting of carnitine deficiency, cytosolic oxidation occurs preferentially leading to the formation of 4-en-valproic acid [40]. The latter has been linked to hepatic injury as well as hyperammonaemia in as much as it causes microvesicular steatosis, a histological hallmark of valproate-induced liver injury.

The incidence of clinically significant hepatic dysfunction with phenytoin is estimated to be 1 in 100 000 persons exposed. The risk of valproate-induced hepatotoxicity is generally low, about 1 in 37 000 in exposed children younger than 2 years of age and even less in adults [41,42]. However, among the group of selected high-risk individuals, the incidence may be as high as 1 in 500 [42]. The risk of valproate hepatotoxicity is highest among children younger than 2 years of age on AED polytherapy and with underlying mental retardation and developmental delay indicative of organic brain disease or inborn errors of metabolism. Intercurrent infections have also been identified as a risk factor in some studies [43]. The toxic hepatitis manifests within 2–3 months of commencement of valproate therapy with non-specific clinical features including lethargy, anorexia, nausea, vomiting and jaundice. Serum levels of AST, ALT, ALP and GGT are elevated several times above the upper limit of normal. Hyperammonaemia is also noted, though when detected as an isolated finding is not indicative of underlying toxic hepatitis.

Although the finding of serious hepatic dysfunction during AED treatment should certainly arouse suspicion of AED-induced damage, intercurrent infectious and alcoholic hepatitis are probably more common. Thus, viral studies should constitute part of the standard workup of hepatitis developing during AED treatment. The settings for both phenytoin- and valproate-induced hepatitis are, however, fairly characteristic and should be easily recognized by the treating physician. The management comprises promptly discontinuing the offending AED and instituting appropriate liver-specific supportive treatment. The use of carnitine in valproate-induced hepatitis is appealing in view of its role in the mitochondrial oxidation of valproate. A consensus panel recommended its use in valproate-induced toxic hepatitis as well as primary carnitine deficiency [44]. The routine co-administration of carnitine with valproate treatment in order to prevent hepatotoxicity is, however, not justified [39].

Epilepsy and thyroid disease

Abnormalities in thyroid function tests have been shown to occur during treatment with several AEDs, including carbamazepine and valproate [45–47]. However, the reported abnormalities lack consistency across published literature. Most studies suggest subclinical hypothyroidism due to carbamazepine and valproate. Apparently, the abnormalities revert upon withdrawal of the AED. The effects have been variously attributed to the enzyme-inducing effects of carbamazepine, an immunological mechanism or also an effect of the AEDs on the hypothalamic centres regulating thyroid function. Although the clinical implications of the thyroid function abnormalities due to AEDs remain uncertain, the effect may be significant in individuals with pre-existing thyroid disorders. In such individuals, an AED without demonstrated effects on thyroid function may be preferred. Data regarding the effect of newer AEDs on thyroid function are extremely limited.

Multiorgan dysfunction

The management of seizures in individuals with multiorgan dysfunction, often in the intensive care unit, is a complicated issue. While it is imperative to rapidly control seizures, the potential consequences of treatment of seizures on the already compromised function of various organs need to be carefully considered. The AEDs may interact with, or simply add to, the complications produced by the complex therapeutic regimen administered for the multiorgan dysfunction. Furthermore, since patients with multiorgan dysfunction are on multiple classes of drugs, the interaction of a particular drug with AEDs may be influenced by the administration of other medications and hence become compli-

cated and unpredictable. In addition, multiorgan dysfunction in the intensive care unit is often complicated by hypotension, systemic acidosis and hypoproteinaemia. In the presence of hypotension, parenterally administered phenytoin, fosphenytoin, phenobarbital, pentothal, midazolam and propofol should be either given with caution or avoided. Continuous electrocardiographic and haemodynamic monitoring is warranted during the administration of these agents. As far as is known, intravenous valproate and levetiracetam are safe in the presence of hypotension. In the presence of acidosis, certain AEDs that may worsen acidosis, for instance topiramate, propofol and lorazepam (due to the excepient, propylene glycol) in high doses, should be avoided [48–50]. If hypoproteinaemia is associated, the estimations of total drug concentrations in the serum of highly protein-bound AEDs, although widely available, do not accurately reflect free AED concentrations. As a result, total drug concentrations may be normal but free drug levels may be elevated, potentially leading to drug toxicity. Hence, estimation of free drug levels is recommended. Finally, since AEDs are eliminated either through the renal or hepatic route, the combined occurrence of renal and hepatic failure invariably leads to drug accumulation and toxicity. Hence dosage considerations are extremely complicated and should be guided by vigilant observation of the clinical response (i.e. seizure control) and side-effects and frequent monitoring of the free AED concentrations.

Organ transplantation

There is a high incidence of new-onset seizures in kidney, liver and cardiac transplant recipients [51,52]. Diagnostic evaluation of new-onset seizures is somewhat specialized and involves considerations other than the common causes of new-onset seizures in the general population. In addition, individuals with prior epilepsy may happen to be candidates for transplant procedures. A major concern in transplant recipients is related to the administration of immunosuppressive agents, including ciclosporin and tacrolimus. Toxicity due to ciclosporin can result in seizures as one of the features of the reversible posterior leucoencephalopathy syndrome (other features of this condition include hypertension, cortical blindness and mutism). Magnetic resonance imaging (MRI) reveals posterior dominant hyperintensities that do not show up on diffusion-weighted imaging, suggesting that these represent vasogenic oedema. High ciclosporin levels in the serum, in addition to hypomagnesaemia and hypocholesterolaemia, provide laboratory support for the diagnosis of this condition. Tacrolimus can also cause seizures, though imaging abnormalities due to tacrolimus intoxication are more often diffuse rather than posterior [53]. The management of seizures associated with toxicity of immunosuppressive agents toxicity consists in lowering blood pressure, omitting the agents and then modifying their dose according to serum concentrations.

Many of the immunosuppressive agents used in the post-transplant period have a narrow therapeutic index and exhibit considerable inter-individual variation in their pharmacokinetics. Ciclosporin, tacrolimus, sirolimus and glucocorticoids are metabolized by the hepatic CYP enzyme systems and hence are susceptible to the inducing effects of the enzyme-inducing AEDs. Carbamazepine, phenytoin and oxcarbazepine reduce blood levels of ciclosporin, tacrolimus and glucocorticoids, thereby compromising their efficacy and fuelling concerns about their potential to cause transplant rejection [54,55]. There is experimental evidence that ciclosporin may also interact with AEDs through its effect on the P-glycoprotein group of drug transporters [56] but the clinical significance of this interaction is unclear. Newer AEDs that have no effect on the hepatic CYP system may be used, although experience with their use in transplant recipients is extremely limited. Levetiracetam holds promise, though there are concerns about an increased risk of infections during its use that may be relevant to the transplant population [57]. The other immunosuppressive agents – mycophenolate mofetil, OKT3 and azathioprine – do not appear to have any significant interaction with AEDs [52].

Cancer and epilepsy/seizures

Both epilepsy and cancer are common disorders and can occur by chance in a proportion of the general population. However, seizures and epilepsy may occur for the first time in people with cancer and their occurrence should lead to consideration of causes that are considerably different from those in the general population [58]. Conversely, the occurrence of cancer in people with epilepsy raises the possibility that the former is, at least in part, due to the carcinogenic potential of AEDs, lifestyle factors associated with epilepsy (e.g. smoking and alcohol ingestion) or a shared biological predisposition to cancer and epilepsy [59]. A common clinical issue is the variety of pharmacokinetic interactions between AEDs and anti-cancer medication which can alter cancer treatment and hence prognosis. Finally, the occurrence of cancer may modify the treatment and prognosis of epilepsy in some instances.

The true incidence of new-onset seizures in people with cancer is not known. Limited data available from specialist cancer centres suggest that seizures occur in nearly 15% of the selected population [60,61]. There appear to be some differences between adults and children with regard to the incidence and aetiology of seizures [61,62]. In children with cancer, there is a high frequency of seizures associated with the use of high-dose myelo-ablative treatment (busulphan) offered for the treatment of childhood leukaemia. In adults with solid cancers, intracranial (parenchymal or uncommonly leptomeningeal) metastasis may frequently be the cause of seizures. Hence, the occurrence of seizures should prompt imaging studies with gadolinium-enhanced MRI to rule out brain metastasis. Anti-cancer drug-induced seizures and metabolic disturbances are the other common causes of seizures in individuals with cancer. Indeed, seizures constitute a dose-limiting toxicity of several anti-cancer agents. Their occurrence is dose dependent and hence, in clinical oncological practice, seizures are encountered due to inadvertent overdosing, the administration of high doses of anti-cancer agents (e.g. busulphan and chlorambucil) as a component of myelo-ablative treatment in preparation for bone marrow transplantation or in the presence of renal or hepatic failure wherein routine doses may lead to toxicity.

The treatment of seizures and epilepsy in people with cancer requires several special considerations. Seizures provoked by drugs and metabolic disturbances do not require long-term AED treatment. In the treatment of acute seizures, a drug with a rapid

onset of action and parenteral formulation is preferred. Parenteral lorazepam (0.05 mg/kg, intravenous) may be administered slowly in order to terminate repetitive or prolonged seizures. Brief and isolated seizures due to drugs or metabolic disturbances do not require treatment. In other situations, if AEDs are required, a loading dose may be administered by the parenteral route as the absorption of oral AEDs is erratic and compromised due to the damaging effects of anti-cancer agents on the gastrointestinal mucosa. Parenteral formulations are available for phenytoin, phenobarbital, valproate and levetiracetam.

Oral benzodiazepines (lorazepam or clonazepam) are routinely administered prophylactically before and until 24 h after high-dose busulphan, given as myelo-ablative treatment prior to bone marrow transplantation in view of the high incidence of seizures associated with this treatment [63].

Many conventional AEDs (phenytoin, phenobarbital, primidone and carbamazepine) are potent inducers and some of the newer AEDs (topiramate and oxcarbazepine in higher doses) are mild inducers of hepatic microsomal enzyme systems and several anti-cancer agents are metabolized to active or inactive products in the liver. As a result, the enzyme-inducing AEDs may induce the metabolism of several anti-cancer agents (including methotrexate, busulphan, vincristine, tenopuside, paclitaxel, irinotecan and topotecan) [64,59]. The clinical implications of the interactions between enzyme-inducing AEDs and several anti-cancer agents are uncertain. On the basis of pharmacokinetic data, up to 1.5 times higher doses of the anti-cancer agents (e.g. paclitaxel) are recommended when given concomitantly with enzyme-inducing AEDs [65,66]. Besides, in dose-determining (phase I) trials of novel anti-cancer agents, higher maximally tolerated doses of the agents are employed in conjunction with enzyme-inducing AEDs [67]. Finally, there is the possibility that the administration of hepatic enzyme-inducing AEDs may adversely impact cancer survival and remission rates by producing subtherapeutic levels of anti-cancer agents due to induction of their metabolism and, hence, an insufficient cytotoxic effect on cancer cells [68].

The spectrum of adverse effects to AEDs as well as anti-cancer agents is also altered by their concomitant administration. For instance, a high incidence of anticonvulsant hypersensitivity syndrome has been reported with phenytoin use in conjunction with cranial irradiation for metastatic brain tumours [69]. Haematological toxicity due to cisplatin is enhanced when used in conjunction with valproate due to compounding of the potential of both agents to cause thrombocytopenia and increased levels of former as a consequence of valproate-induced hepatic enzyme inhibition [70].

Newer AEDs that do not induce hepatic microsomal enzyme systems (e.g. gabapentin and levetiracetam) may be the preferred AEDs for seizure control in individuals with cancer. Clinical experience with these newer AEDs is now growing and, hopefully, therapeutic strategies for seizure control based on their use will soon emerge [71]. Conventionally, surgical treatment for intractable epilepsy is often disregarded in individuals with cancer owing to their limited survival. However, with the prospects of lasting remission in several cancers, particularly childhood leukaemia, surgical treatment becomes an appealing option in the management of intractable epilepsy in individuals with cancer [72].

Infections and epilepsy

A number of infectious disorders involving the central nervous system (CNS) may cause seizures and epilepsy and, conversely, infectious disorders can occur during the course of chronic epilepsy.

Acute CNS infections are the cause of both acute symptomatic as well as unprovoked seizures. In community-based samples, the incidence of acute symptomatic seizures due to CNS infections is 5.2 in 100 000 person-years [73]. CNS infections may account for as many as 15% of new-onset acute symptomatic seizures. The 20-year risk of unprovoked seizures after an acute CNS infection episode varies between 2.4% and 22% [74]. The risk depends on the nature of the infection, its site and severity. It is high, for instance, following severe herpes simplex encephalitis because of the involvement of the highly epileptogenic mesial temporal cortices, but may be much lower in mild cases. The risk is also increased with the occurrence of early seizures during the acute CNS infection episode and particularly so with the occurrence of status epilepticus [74,75]. In community-based samples of newly diagnosed epilepsy, CNS infections may be responsible for at least 3% of all cases [76]. The figures quoted here are largely derived from the Rochester community in the USA. The incidence and attributable risk is different in other parts of the world because of disparity in the incidence and pattern of CNS infections throughout the world [77].

The incidence, course and outcome of epilepsy following an acute CNS infection episode have not been systematically studied. On the basis of limited data derived from highly specialized epilepsy centres, it may be inferred that both acute bacterial meningitis and viral encephalitis constitute antecedent illnesses for the development of intractable mesial temporal lobe epilepsy with underlying hippocampal sclerosis [78]. In addition, neocortical epilepsy occurs frequently following viral encephalitis but not after bacterial meningitis [79]. Regardless of the nature of the antecedent illness, the prognosis of surgical cure is good in cases in which unilateral mesial temporal sclerosis is demonstrated on MRI [80].

Human immunodeficiency virus infection and seizures

Seizures are common in human immunodeficiency virus (HIV) infection, though their precise frequency varies according to the source population. They typically occur in the later stages of HIV infection. However, on occasion, they may constitute the presenting manifestation of HIV infection [81]. A variety of opportunistic infections such as toxoplasmosis and CNS tuberculosis and primary CNS lymphoma may be the cause of seizures in HIV-seropositive individuals. Other conditions, for example progressive multifocal leucoencephalopathy, cryptococcal meningitis, drugs and metabolic disturbances, may also rarely cause seizures. In about half of HIV-infected individuals, no additional cause for seizures can be identified. In these individuals, the primary HIV infection itself is considered to be the cause of seizures [82]. Regardless of the cause, recurrence rates after new-onset seizures in HIV infection are high. Hence, long-term AED treatment is advocated except when reversible metabolic derangements are identified to be the cause of seizures.

Since HIV-infected individuals have multiple co-morbidities and are often on several medications for the treatment of primary HIV infection as well as for the prophylaxis and treatment of several opportunistic infections, several drug–drug and disease–drug interactions should be carefully considered in making the choice of AED. Gastrointestinal disorders occur frequently in HIV infection and these may impair the absorption of AEDs across the gastrointestinal mucosa. Hypoalbuminaemia in HIV infection may alter protein binding of several AEDs and hypergammaglobulinaemia may signify altered immune status, leading to an increased frequency of allergic reactions to many AEDs [83]. Of the antiretroviral agents, the class of drugs known as protease inhibitors is metabolized by hepatic CYP3A4 and is hence a target for enzyme induction by the enzyme-inducing AEDs including phenobarbital, phenytoin and carbamazepine. The result of these drug interactions is a reduction in plasma concentrations of the antiretroviral agents, potentially leading to increased viral replication and the emergence of drug resistance [83]. An interaction between valproate and zidovudine as a result of hepatic microsomal enzyme inhibition by the former has also been reported [84]. In addition, valproate has been found to stimulate HIV replication *in vitro* [85]. Although the effect has not been replicated *in vivo*, caution is still advised in the use of valproate in HIV-infected individuals [86]. Newer non-enzyme AEDs such as levetiracetam and gabapentin hold promise in view of their inconsequential enzyme-inducing ability and low levels of protein binding. At present, however, clinical experience with their use is extremely limited and their availability in the majority of the regions where HIV infection is most widely prevalent is unpredictable.

Cysticercosis and epilepsy

Infestation of the brain parenchyma by the larval stage of the pork tapeworm, *Taenia solium*, is the main cause of late-onset epilepsy in much of the developing world [87]. Several epidemiological studies in Central and South America have established that roughly one-third of all epilepsies in the community may be attributable to cysticercosis [88]. In addition, the parasitic infestation has been documented in large numbers in parts of South and South-East Asia and sub-Saharan Africa.

Seizures are the most common presenting manifestation of brain parenchymal infestation with cysticerci [89]. Presumably, these occur as a manifestation of host brain parenchymal inflammatory response to degenerating cysticerci. Hence, the majority of the seizures appear to be provoked by brain inflammation and the long-term prognosis for seizure control is generally good [90,91]. However, there may be a subgroup of individuals in whom seizure remission may be difficult to achieve [92]. Factors that have been identified with an increased risk of seizure relapse include persisting brain cysticercal lesions and residual calcific lesions. In addition, an association with mesial temporal sclerosis has been suggested but it remains to be seen if this association is causal [93].

Treatment of cysticercosis comprises the administration of anthelminthic agents (including albendazole and praziquantel), corticosteroids and AEDs. Albendazole (15 mg/kg/day) is most frequently used for varying periods, usually 7–28 days. Benefits of anthelminthic treatment have been demonstrated in the form of superior rates of cyst resolution as well as improved seizure control over short periods of time (usually a few months) in several small, placebo-controlled trials [94,95]. In addition, treatment with a short course (2 weeks) of corticosteroids alone, as well as in combination with anthelminthic agents, has been shown to improve seizure control over 6–9 months [96]. AEDs are administered to all individuals presenting with seizures. Data emerging from observational studies suggest that AEDs should be administered until such a time as imaging shows no active or inflammatory degenerating parenchymal cysticercal lesions [97].

In the subgroup of those with solitary cysticercus granuloma that usually resolves over 3–6 months following initial presentation with seizures, AEDs can be withdrawn after complete resolution is demonstrated on imaging studies [92]. A slight increase in frequency of seizures has been noted during the course of anthelminthic treatment owing to brain parenchymal inflammation provoked by the anthelminthic agent-induced degeneration of the cysticerci [94]. Therapeutic considerations also include potential drug–drug interactions between anthelminthic agents and AEDs (in particular, the enzyme-inducing AEDs). Significant reductions in the maximal plasma concentration and area under concentration–time curve of the active metabolite of albendazole (i.e. albendazole sulphoxide) has been demonstrated with concomitant administration of phenytoin, phenobarbital and carbamazepine) [98].

Tuberculosis and epilepsy

Seizures may occur in CNS tuberculosis for a variety of reasons. These include the presence of brain parenchymal tuberculoma or cortical infarcts due to vasculitis; the use of antitubercular agents such as isoniazid; metabolic disturbances such as hyponatraemia as a result of salt wasting; or inappropriate antidiuretic hormone secretion. Early seizures are fairly common in tubercular meningitis, but late seizures are less common [99,100]. The frequency of late seizures may be underestimated, as there are very few long-term follow-up studies of tubercular meningitis and none have specifically reported rates of epilepsy.

Drug interactions between antitubercular agents and enzyme-inducing AEDs need to be considered in the treatment of tubercular meningitis. Isoniazid induces the metabolism of several AEDs and, on the other hand, rifampicin inhibits the metabolism of many AEDs [101]. The combined administration of the two antitubercular agents (i.e. rifampicin and isoniazid), both of which are standard components of virtually every antitubercular regimen, can produce unpredictable responses. There are also concerns that AEDs may predispose to isoniazid-induced hepatitis, a common adverse effect of antitubercular treatment [102]. Finally, hepatitis complicating antitubercular therapy may precipitate AED toxicity due to impaired hepatic clearance of the latter [103].

Connective tissue disorders

Seizures and/or epilepsy may occur in several connective tissue disorders but have been most characteristically reported in systemic lupus erythematosus (SLE). These occur in 10–15% of hospital-based populations of SLE [104,105]. Diverse

mechanisms may underlie the occurrence of seizures in SLE, including antineuronal antibodies, vascular infarctions, metabolic disturbances and complicating CNS infections. Not infrequent is the occurrence of posterior reversible leucoencephalopathy syndrome in SLE, perhaps due to hypertensive crises complicating the disease [106]. Typically, the occurrence of seizures correlates with disease activity. Correlation has also been noted with other neuropsychiatric presentations of SLE and the demonstration of antiphospholipid antibodies in sera of individuals with SLE [104,105]. In case–control studies of people with epilepsy, however, no association with antiphospholipid antibodies has been noted [107].

The incidence of late unprovoked seizures (or epilepsy) appears to be fairly low in SLE. Effective immunological treatment of the active disease appears to have a favourable impact on seizure control, though long-term AED treatment may be required in many cases. Although chloroquin is known to cause seizures, its administration has not been associated with an increased risk for seizures in SLE. If long-term AED is required, one of the newer, non-enzyme-inducing AEDs may be the preferred option, as patients with SLE may require multiple classes of medications (e.g. corticosteroids, the levels of which are reduced by concomitant administration of enzyme-inducing AEDs).

Pulmonary and respiratory disease

Neurogenic pulmonary oedema is a rare complication of seizures and status epilepticus but is noteworthy as it may be one of the mechanisms by which sudden death occurs in epilepsy (SUDEP) [108]. It occurs within a few hours of the seizure and may present with dyspnoea, breathing difficulty and haemoptysis, leading to cardiovascular collapse. A surge in circulating sympathomimetic amines coincident to the seizure discharge leads to increased vasomotor tone and hence left ventricular failure and an increased pulmonary vascular permeability. Management comprises intensive cardiopulmonary support.

The administration of the bronchodilator agent theophylline in pulmonary airway disease can result in seizures. Seizures attributable to theophylline usually occur in extremes of age and in the context of overdosage but have also been reported with serum levels of theophylline that are within the therapeutic range [109]. Caution is recommended during the administration of theophylline in individuals with known epilepsy.

Obstructive sleep apnoea represents a significant co-morbidity in people with epilepsy. The exact incidence of sleep apnoea in populations with epilepsy has not been determined. However, based on studies of highly selected populations of epilepsy, it has been suggested that sleep apnoea is frequent in people with epilepsy. The converse (i.e. an altered incidence of epilepsy in individuals with sleep apnoea) need not necessarily be the case [110,111]. The high frequency of sleep apnoea among people with epilepsy may be due to a depressive effect of nocturnal seizures and AEDs on airway muscular tone and weight gain associated with some of the AEDs. In individuals with co-morbid epilepsy and obstructive sleep apnoea, the treatment of sleep apnoea with continuous positive airway pressure (CPAP) ventilation has been shown to improve seizure control [112,113]. Evidence for the reverse (i.e. improvement in sleep apnoea with treatment of epilepsy) has also been presented [114].

An interesting related disorder is sleep-disordered breathing with compromised airflow in step with the stimulation-on periods during vagus nerve stimulation [115]. The degree of air flow impairment is usually mild but may be of significance in subjects with pre-existing obstructive sleep apnoea. Therefore, ideally, candidates for vagus nerve stimulation should be screened for obstructive sleep apnoea prior to implantation. Clinically significant sleep-disordered breathing during vagus nerve stimulation usually responds to reduction of stimulation intensity of current and increasing the duration of off-periods. Rarely, CPAP ventilation may be required [115].

Cardiac disease

A bidirectional cause–effect relationship exists between cardiac disorders and epilepsy; cardiac disorders may cause epilepsy and, conversely, epilepsy or its treatment may potentially result in cardiac disorders. Two types of cardiac disorders (i.e. cardiac arrhythmias and ischaemic cardiovascular disease) are discussed in detail below. In addition, hypotension is a well-known adverse effect of intravenously administered phenytoin and fosphenytoin [116,117]. In the case of phenytoin, hypotension is frequently encountered when rates of infusion are in excess of 50 mg/min or in critically ill (e.g. severe sepsis) patients [118]. The manufacturer's product insert advises caution in the intravenous administration of phenytoin in the presence of hypotension. Phenytoin-induced hypotension usually responds to fluid administration, pressor agents, elevation of the foot end of the patient and reducing the rate of infusion.

Cardiac arrhythmias

The exact incidence of cardiac arrhythmias in epilepsy is not known. Available reports are mostly of studies in highly selected populations of epilepsy and hence may represent an overestimate. Nonetheless, these reports are significant as cardiac arrhythmias may account in part for SUDEP in people with epilepsy. A variety of potentially life-threatening cardiac arrhythmias have been described in epilepsy, including cardiac asystole, sinus node arrest, atrioventricular conduction defects, supraventricular tachycardia, ventricular tachycardia and ventricular fibrillation [116,119–121]. These have been documented both during seizures (in particular, complex partial seizures) and in the interictal period [122–124]. The most common cardiac rhythm disorder during complex partial seizures, however, is sinus tachycardia, as is commonly noted in electrocardiographic recordings made during seizures in epilepsy monitoring units. Ictal asystole has been seldom documented [124]. QT interval abnormalities have been documented during interictal epileptiform discharges [125]. Although poorly researched, QT interval prolongation may also occur as a consequence of AED (such as carbamazepine and phenytoin) administration [126–128]. The QT interval abnormalities may predispose to lethal ventricular tachycardias and have been proposed to underlie a proportion of cases of SUDEP.

There are many factors influencing the occurrence of cardiac rhythm disorders in epilepsy. Arrhythmias linked to ictal events

and interictal discharges may be attributable to activation of the amygdala through its connections with the sympathetic centres in the hypothalamus [129]. An intense sympathetic discharge during seizures may be the basis of ictal tachycardia, while excessive parasympathetic discharge may lead to ictal asystole. A common genetic basis of cardiac rhythm disorders and epilepsy has been suggested, referring to potassium and sodium ion channel disorders that may underlie both certain forms of epilepsy as well as the inherited long QT syndromes [130,131]. Structural cardiac abnormalities, including mild fibrosis of the cardiac conduction system, have been described in autopsy studies of SUDEP, but the cause and significance of these appear uncertain [132]. AEDs have been implicated in the generation of arrhythmias. Atrioventricular conduction defects are a recognized complication of carbamazepine, phenytoin and fosphenytoin administration and usually revert following withdrawal of the drug. In addition, reduced variability of heart rate and lengthening of the QT interval have been reported with the use of carbamazepine and phenytoin in some studies but have not been substantiated in others. Barbiturates and most of the newer AEDs appear not to cause cardiac conduction defects or QT interval prolongation [133]. Finally, uncommon cardiac disorders such as the inherited long QT syndromes, which often lack overt cardiac symptoms, may masquerade as epilepsy [134]. Key differentiating features of these conditions include the occurrence of syncopal episodes without seizures, precipitation by exercise and a family history of sudden death.

A baseline electrocardiogram should be ordered prior to commencement of AED treatment, with attention directed to existing cardiac conduction and QT interval abnormalities. In the presence of cardiac conduction defects and possibly also QT prolongation, carbamazepine and phenytoin are best avoided. Barbiturates, valproate and most of the newer AEDs appear to be safe in these situations. If, during treatment with carbamazepine or phenytoin, cardiac conduction defects are detected, then these drugs should be withdrawn and replaced with alternative AEDs. The documentation of ictal asystole or tachyarrhythmia in refractory epilepsy may require insertion of a cardiac pacemaker or automatic implantable cardiac defibrillator [135].

Ischaemic cardiovascular disease

Although early studies suggested that the risk of ischaemic cardiovascular disease was decreased in people with epilepsy, a small number of recent studies have refuted this contention and have demonstrated an increased prevalence of cardiovascular disorders in people with epilepsy [2,4,136]. If the risk of cardiovascular disease were increased in epilepsy, this could be due to lifestyle factors – for instance obesity, altered smoking and drinking habits and sedentary lifestyle – all of which are more common in people with epilepsy [137–139]. In addition, the administration of AEDs may contribute to an increased cardiovascular morbidity through their effect on homocysteine levels and serum lipid composition. Elevations of serum homocysteine levels have been consistently documented during administration of the enzyme-inducing AEDs, including phenytoin, carabamazepine and phenobarbital [140]. The literature regarding the effect of valproate is inconsistent and regarding newer AEDs is scanty [141]. The amino acid homocysteine is closely linked to other amino acids, including cysteine and methionine. Deficiencies of the vitamins B_{12} and B_6 and folic acid lead to increased levels of homocysteine. Elevated levels are associated with an increased risk of ischaemic heart disease, stroke, peripheral vascular disease and venous thrombosis in a graded manner [142]. The degree of elevation of homocysteine levels by the enzyme-inducing AEDs is mild in comparison with some of the genetic disorders responsible for hyperhomocysteinaemia. In addition, the elevated levels during treatment with enzyme-inducing AEDs are accompanied by reduced levels of serum or erythrocyte folate and serum vitamin B_{12}, and pyridoxal phosphate (vitamin B_6). Hence, correction of the accompanying deficiencies by vitamin supplementation may sound an appealing strategy to lower homocysteine levels. However, folic acid or other vitamin supplementation has not been shown to confer a reduced risk of cardiovascular disease in the general population and hence cannot be recommended in people using AEDs [143,144]. Besides the effect of enzyme-inducing AEDs on serum homocysteine levels, there are also concerns about their effect on serum lipid composition. About three-quarters of the cholesterol in the human body is endogenously synthesized, primarily in the liver. As a result, the enzyme-inducing AEDs may step up the hepatic synthesis of cholesterol, thereby increasing the risk of cardiovascular and cerebrovascular events. Longitudinal studies in users of enzyme-inducing AEDs have not, however, demonstrated any consistent effect of the AEDs on the lipid profiles [145,146]. The routine monitoring of serum lipid composition is not recommended in people with epilepsy. Individuals with epilepsy who are on enzyme-inducing AEDs should follow the recommendations regarding monitoring and control of serum lipids as for the general population.

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21 Psychiatric Features of Epilepsy and their Management

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Epilepsy was for many years classified as and considered a 'psychiatric disease', no doubt because of the frequent association of seizures with psychiatric symptoms. In recent times, the physical basis of epilepsy has been emphasized and the psychological and psychiatric features conceptualized as 'co-morbidities'. That there is a close and intimate relationship between the physical and the psychiatric features of epilepsy, however, cannot be denied, and to what extent they are an integral part of the condition or a co-morbidity is arguable. The management of the psychiatric symptoms of epilepsy forms a very important part of modern clinical practice. In this chapter, these psychiatric symptoms are considered under the same broad headings used in conventional psychiatry. However, as will be emphasized, the psychiatric presentations in epilepsy often differ from those encountered in the functional psychiatric disorders.

Affective and anxiety disorders

Affective and anxiety disorders are the most common psychiatric disorders occurring in people with epilepsy. These International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [1], or *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV) [2], categories include manic, depressive, dysthymic, cyclothymic and bipolar affective disorders within the affective subgroup and generalized anxiety disorder (GAD), panic disorder and obsessive–compulsive disorder (OCD) among the anxiety disorders. Many patients with epilepsy, furthermore, suffer from atypical affective disorders which fail to meet established diagnostic criteria. Examples include the interictal dysphoric disorder and the abnormal affective and psychotic states brought about due to a reduction in or abolition of seizures (i.e. forced normalization) or due to the adverse effects of antiepileptic drugs (AEDs).

Not only are these disorders important to diagnose and treat in their own right but their presence also has implications for the treatment of the epilepsy itself. Hitiris *et al*. [3], for example, have shown that pharmacoresistance, in a large cohort followed for over 20 years, was associated with prior or current psychiatric co-morbidity and intermittent recreational drug use. Anhoury *et al*. [4] found that 'patients with a preoperative psychiatric history and de novo psychiatric symptomatology had a poorer surgical outcome in terms of seizure frequency', and Kanner *et al*. [5] noted that a lifetime history of depression is a predictor of failure to reach post-surgical (anterior temporal lobe) seizure outcome, free of auras and disabling seizures.

Prevalence of affective disorders in epilepsy

Estimates of the incidence and prevalence of affective disorders in epilepsy vary widely. Lifetime prevalence for a major depressive episode in the general population ranges between 3.7% and 6.7%. In patients with epilepsy, rates range from 11% (current depression) to 62% (lifetime-to-date depressive disorder) with an estimated mean of 30% across studies [6,7]. Prevalence may be lower (3–9%) in patients with good seizure control [8]. Anxiety disorders are also more frequent in this population and have been reported in 10–25% [7]. Mixed anxiety and depressive disorders have been reported to occur in 8.5% [9].

The prevalence of bipolar symptoms and past diagnoses of bipolar I or II disorder among patients with epilepsy was investigated by Ettinger *et al*. [10]. They found bipolar symptoms to be present in 12.2%; almost half of these 'screen-positive' patients were subsequently diagnosed with bipolar disorder.

The 'bidirectional relationship' between epilepsy and depression

Much research recently has addressed the issue of whether or not the relationship between epilepsy and depression is 'bidirectional'. This is not a new idea. Twenty-six centuries ago, Hippocrates wrote 'melancholics ordinarily become epileptics, and epileptics melancholics' [11]. In 1901, Sir William Gowers wrote that 'Suicide although not a certainty is often a probable indication of a morbid family tendency and some weight must be given to it as an indication of a disposition to a disease of which epilepsy may be the result even when it has an immediate exciting cause' [12].

Recent work supports this view. The main findings are:

- Adults with late-onset epilepsy (>54 years) are 3.7 times more likely to have a history of depression than are control subjects [13].
- Those with new-onset epilepsy are seven times more likely to have a history of depression than control subjects and the risk may be even higher (as much as 17-fold) in those with focal epilepsy [14].

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- Children with new-onset epilepsy are four times more likely to have had a depressive episode prior to the first seizure [15].
- Adults and children over 10 years of age with a first unprovoked seizure or newly diagnosed epilepsy were found in one study to be five times more likely to have a history of attempted suicide [16].

Depressive symptoms associated with seizures

The occurrence of preictal affective symptoms has received relatively little attention in the literature. It is, nevertheless, clear that many patients with focal seizures do report prodromal states of depression, irritability or anxiety occurring hours to days before a seizure.

Simple or complex partial seizures affecting limbic structures have been associated with the production of numerous affective (fear, anger, depression, sexual excitement) symptoms, many of which have been recorded using intracranial stereoelectroencephalography (SEEG) techniques in patients during seizures [17] or by electrical stimulation of depth electrodes [18]. Ictal fear or panic is brief, lasting less than 30 s. It occurs out of context to concurrent events and may be seen in both temporal and extratemporal epilepsy, although it is more common in the former [19]. It can be severe, and can be confused diagnostically with primary panic attacks, which are also common in patients with epilepsy [20]. Ictal depression may range from mild feelings of sadness to profound hopelessness and despair. The potential for induction, by high-frequency electrical activation, of a depressive state was well demonstrated by Bejjani *et al*. [21], who induced a transient period of acute depression within 5 s of stimulating the left substantia nigra using deep brain stimulation (DBS) in a 65-year-old woman with a 30-year history of Parkinson's disease. This state resolved quickly with termination of the stimulation, but during this episode she started to cry and felt guilt, uselessness and hopelessness, and commented, 'I no longer wish to live, see anything, hear anything . . . I'm fed up with life . . . I'm disgusted with life . . . I don't want to live any more.'

A variety of postictal affective symptoms can occur following individual seizures or clusters of seizures. Kanner *et al*. [22] examined 100 consecutive patients with refractory epilepsy during the postictal period and found that symptoms of depression occurred in 43%, anxiety in 45%, hypomania in 22%, and active and passive suicidal thoughts in 8% and 13%, respectively. There was a significant association between a prior history of depression and symptoms of hopelessness, suicidal ideation, self-deprecation and guilt, and the median duration for most symptoms was 24 h.

Affective disorders in epilepsy

According to ICD-10, the main features of a depressive episode include: (1) lowered mood; (2) reduced energy and concentration; (3) diminished capacity for enjoyment, or interest; (4) marked tiredness after minimal effort; (5) disturbed sleep (hypersomnia or insomnia); (6) reduced appetite and weight loss (DSM-IV specifies a change of 5% of body weight over a 1-month period in the absence of dieting); (7) self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present; (8) the lowered mood varies little from day to day and is unresponsive to circumstances; (9) 'somatic' symptoms may be present and include early-morning waking, diurnal variation in mood (worst in morning), psychomotor retardation/agitation and loss of libido; (10) recurrent thoughts of death and suicide are common with an increase in severity of the depression; (11) in severe forms there may be delusions, hallucinations and stupor. DSM-IV specifies that five or more symptoms should be present nearly every day over the same 2-week period and represent a change from previous functioning; at least one of the symptoms must be either low mood or loss of interest and pleasure anhedonia. Whilst depressive episodes which fulfil these criteria do occur frequently in patients with epilepsy, this is not always the case and a range of atypical affective disorders may also occur.

Atypical affective disorders in epilepsy

A significant proportion of depressive disorders in epilepsy fail to conform to current diagnostic criteria [23]. In a review of 97 patients with epilepsy whose depression was severe enough to warrant pharmacological treatment, Kanner *et al*. [24] found that in only 29% were the DSM-IV criteria for a major depressive disorder met.

The most common 'atypical' affective disorder in epilepsy is a chronic intermittent interictal dysphoric syndrome. A symptom complex similar to this was first described in 1923 by Emil Kraepelin, who used the term *Verstimmungszustand* to emphasize the periodicity of the dysphoric mood changes seen in these patients, along with irritability and outbursts of aggressive behaviour [25]. These dysphoric states were felt to occur 'very frequently with utter disgust of life and suicidal bent' [26]. The key symptoms included (1) irritability, (2) low mood, (3) insomnia, (4) anxiety and (5) occasional euphoria, and could last anything from a few hours up to a couple of days, at frequencies varying between every few days and every few months. This concept has since been elaborated upon by Blumer, who listed six key symptoms: (1) depressive mood, (2) anergia, (3) pain, (4) insomnia, (5) labile affective symptoms (fear, anxiety) and (6) 'specific' symptoms, which included paroxysmal irritability and euphoria [27]. A recent incarnation of this disorder is the 'dysthymic-like disorder of epilepsy' (DLDE) [9]. The difference between this and a DSM-IV diagnosis of dysthymic disorder lies in the disorder's duration and severity. Whilst several features are held in common (e.g. low mood, anhedonia, poor concentration, guilt, recurrent thoughts of death, a sense of worthlessness, weight loss/gain, insomnia/hypersomnia and psychomotor retardation/agitation), the former diagnosis is characterized by symptom-free periods of 1 to several days' duration, thus precluding a DSM-IV diagnosis. In the study by Kanner *et al*., 71% of their patients with both epilepsy and depression manifested symptoms of DLDE [24]. Anhedonia was the most disabling symptom in around half of these patients, and was significantly associated with a history of major depression. In the remainder, irritability and poor frustration tolerance were the key features.

Recently, Mula *et al*. [25] investigated whether or not this interictal dysphoric disorder is (a) a robust concept and (b) specific to epilepsy. They found that whilst the construct appeared to be robust, the specificity was lacking, and that the disorder can also be seen in other central nervous system (CNS) disorders such as migraine. This notwithstanding, clinical

experience suggests that this disorder is particularly associated with epilepsy.

Generalized anxiety disorder

In ICD-10, GAD refers to 'anxiety that is generalized and persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances (i.e. it is "free-floating")'. DSM-IV specifies that the symptoms must be present more days than not for a period of at least 6 months. The main symptoms include (1) persistent nervousness, (2) trembling, (3) muscular tension, (4) sweating, (5) lightheadedness, (6) palpitations, (7) dizziness and (8) epigastric discomfort. It is often co-morbid with other medical or psychiatric conditions: in a study by Kessler, up to 90% of patients with GAD showed concomitant symptoms of depression, dysthymia, somatization, bipolar disorder or substance abuse [28].

In the general population, the lifetime prevalence of generalized anxiety disorder is 5.1%, with a 12-month prevalence measured at 3.1% [28]. In patients with epilepsy, anxiety symptoms have been reported in up to 66% [29], and Cramer *et al*. found that 48% of their series reported symptoms of anxiety which were rated as moderate in 16% and severe in 7% [30]. Most recently, Schöndienst and Reuber examined 77 patients with medically refractory epilepsy and reported that 12% met the DSM-IV criteria for the diagnosis of GAD [20].

Panic disorder

The essential features of panic disorder as defined by ICD-10 are 'recurrent attacks of severe anxiety (panic), which are not restricted to any particular situation or set of circumstances and are therefore unpredictable'. DSM-IV specifies that there should be at least one attack per week for a period of at least 1 month. It should not be diagnosed in the presence of a co-morbid depressive disorder.

Episodes of interictal panic are more protracted than those seen in the ictal phase, usually lasting from 5 to 20 min but sometimes persisting for several hours. The feeling of fear or panic is very intense ('feeling of impending doom') and associated with a range of autonomic symptoms (tachycardia, blood pressure fluctuation, diffuse diaphoresis and shortness of breath). There may be anticipatory anxiety due to a fear of further attacks and avoidance behaviours may result and significantly limit independence and quality of life. Beyenburg *et al*. [31] estimated that patients with epilepsy were six times more likely to suffer from panic disorder than the general population, with point prevalence estimates ranging between 5% and 30% [32]. It is important to differentiate true panic attacks from partial seizures, which sometimes can have similar symptoms.

Obsessive–compulsive disorder

According to ICD-10, there are two key features of OCD:

1 Recurrent obsessional thoughts are ideas, images or impulses that repeatedly enter the patient's mind in a stereotyped form. These are recognized as the patient's own thoughts, but are felt to be distressing and are usually resisted.

2 Compulsive acts or rituals are stereotyped repetitive behaviours which are not enjoyable and do not result in the completion of useful tasks. Their function is to prevent some objectively unlikely event, often involving harm to or caused by the patient. Resisting the compulsive act usually leads to an immediate increase in anxiety.

Monaco *et al*. [33] compared the prevalence of OCD in 62 patients with temporal lobe epilepsy (TLE), 20 patients with idiopathic generalized epilepsy (IGE) and 82 healthy control subjects. Nine of the TLE patients, none of the IGE patients, and only one of the controls had a diagnosis of OCD. Patients with TLE and OCD differed significantly with respect to a history of depression when compared with patients with TLE without OCD and a recent study comparing the obsessive–compulsive themes in patients with TLE and Tourette's syndrome concluded that the former tend to focus on existential thoughts whereas the latter present themes related to sexuality and impulsiveness [34]. TLE surgery may cause *de novo* OCD [35,36]; however, several authors have also reported complete remission or improvement of OCD following surgery for TLE [37,38].

Suicide in epilepsy

Suicide accounts for about 1.5% of deaths worldwide [39], yet the suicide rate in epilepsy would appear to be much higher. One meta-analysis by Harris and Barraclough [40] found that suicide accounted for for 181 out of 2196 deaths (8%) in epileptic subjects. Others, however, argue that the true rate is lower. More recently several very large cohorts have been followed up for many thousands of patient-years in Denmark, the UK and Sweden, which demonstrate statistically significant standardized mortality ratios of between 3 and 5.5 [41–43]. It has been stated that the lifetime prevalence of suicidal ideation is roughly twice as high among patients with epilepsy as among the general population [44].

Suicide in epilepsy is a rare event and studies need to retain large numbers of people for long periods of time in order to detect statistically significant differences in suicide between epileptic and non-epileptic populations. Two studies, one in the Netherlands [45] and one in Scotland [46], found increased standardized incidence ratios of 2.1 and 1.7 of suicide in patients with epilepsy, but the differences were not statistically significant. World Health Organization (WHO) prevalence figures for suicide vary from country to country and, whilst it is clear that patients with epilepsy in Denmark are more likely to die by suicide (which has a higher baseline prevalence of suicide), these figures may not apply elsewhere [41].

Several risk factors for suicide in epilepsy have been highlighted in the literature and these can be summarized as follows:

1 The highest relative risk (RR) would seem to occur in the first 6 months after diagnosis (RR 5.35), particularly in those with co-morbid psychiatric disease (RR 29.2), even after adjusting for socioeconomic factors (RR 13.7) [41].

2 Use of antipsychotic drugs increases risk 10-fold [47].

3 Early-onset epilepsy (<18 years vs. >29 years) and having any seizure compared with being seizure free in the past year carry respective relative risks of 16.0 and 2.0 [47].

4 TLE has been associated with a 25-fold increase in risk, and for surgically treated patients this may be even higher [40].

5 Of 193 patients followed up after temporal lobectomy for 5–24 years, 9 out of 37 deaths were by suicide. If six further deaths which occurred in unclear circumstances are included, the suicide rate became 50 times that expected [48].

Diagnosis of depression in epilepsy

Ordinarily, the diagnosis of depression is made on the basis of a patient meeting criteria for a depressive syndrome as per ICD-10 or DSM-IV; however, as the above discussion highlights, there are depressive syndromes in epilepsy which do not meet standardized operational criteria. Furthermore, the diagnosis of depression in this particular patient group is complicated by the fact that many patients do not complain of mood problems (or are rarely asked) and the problems with sleep, appetite, libido, cognition or memory can be interpreted as side-effects of antiepileptic drugs. Feelings of guilt and a circadian pattern of symptom severity are rare in epilepsy [23].

Gilliam *et al*. have attempted to address the difficulties in diagnosis by developing and validating the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [49]. This instrument attempts to minimize the confounding effects of adverse events caused by antiepileptic drugs or cognitive problems associated with epilepsy. It includes items relating to core depressive symptoms such as anhedonia, guilt, the feeling that nothing one does is right and that one would be better off dead, and takes only 3 min to complete. It has been validated in patients with epilepsy and a score of ≥15 has a specificity of 90% and sensitivity of 81% for a diagnosis of major depression.

Other potentially useful rating scales include the Beck Depression Inventory (BDI-II) [50], which is a 21-item self-rated screening instrument that takes about 5 min to complete and has also been validated in epilepsy. Scores over 20 indicate moderate to severe depression. Suicidality can be assessed using the suicidality module of the Mini International Neuropsychiatric Interview (MINI) [51].

Treatment of depression in epilepsy

In a random survey of 135 neurologists, Gilliam reports that 82% did not routinely screen epilepsy patients for depression in their outpatient clinics [52]. Others have pointed out that as many as 60% of patients with epilepsy and depression were symptomatic for more than 1 year before any treatment was suggested [24], a finding supported by Wiegartz *et al*. [53], who noted that one-quarter of their patients with partial seizures reported symptoms of minor depressive disorder (dysthymia and depressive disorder not otherwise specified), but none had received treatment.

This could be in part due to the concern that the antidepressant drugs can increase seizure frequency. Tricyclic antidepressants (TCAs) can certainly lower seizure threshold (particularly at higher doses; see below) but the incidence of seizures in people without epilepsy treated with selective serotonin reuptake inhibitor (SSRI), noradrenergic and specific serotonergic (NaSS) and serotonin–noradrenaline reuptake inhibitor (SNRI) antidepressants is actually significantly lower than would be expected in the general population (citalopram, <0.3%; sertraline, 0.0%; fluoxetine, 0.2%; duloxetine, 0.0%; mirtazepine, 0.04%; venlafaxine, 0.1%) with the exception of bupropion IR [54]. Serotonin has been shown to inhibit epileptiform activity in rat hippocampal CA1 neurones via 5-hydroxytryptamine 1A ($5HT_{1A}$) receptor activation, and depresses excitatory postsynaptic potentials in a concentration-dependent manner [55]. Fluoxetine [56] and citalopram [57,58] have been reported to produce antiepileptic effects in open-label studies of non-depressed epileptic patients, reducing seizure frequency by as much as 35–64%, and it may be that seizures which occur after starting SSRIs are merely reflecting the increased risk of seizures associated with the depressive disorder [9]. Assuming the incidence of unprovoked seizures in the general population is 60 per 100 000 patient exposure years [(PEY) the cumulative time in years that a patient is exposed to a drug or placebo], the reported incidence of seizures of 1116.7 per 100 000 PEY in patients treated with placebo in antidepressant clinical trials reviewed by Alper *et al*. is a figure which is approximately 19 times the rate seen in the general population [54].

Tricyclic (particularly high dose) and tetracyclic antidepressants are felt to pose a greater level of risk, and it is recommended in some guidelines that these agents should be avoided altogether if at all possible. However, Blumer and Altshuler [59] treated about 200 depressive epilepsy patients over a period of 20 months, initially with imipramine or amitriptyline at daily doses of less than 150 mg/day. Twenty-two non-responders were then treated in combination with paroxetine 10–50 mg (an SSRI). Fifteen had a complete remission and four a partial response of their depressive symptoms. Only three were refractory to this regimen and there was no exacerbation in seizures. Bupropion (contraindicated in epilepsy, according to manufacturer's prescribing information), clomipramine, amoxapine and maprotiline pose the highest risk of worsening seizures and should be avoided in epilepsy given the wide variety of alternatives available.

Another possible risk is that antidepressant use can 'switch' the depressive into a manic state in patients with hitherto undiagnosed bipolar disorder presenting with depression as the index episode. There are certain features in the history that should act as a red flag for this possibility and would warrant specialist referral before initiating antidepressant therapy: (1) prepubertal, adolescent or postpartum onset; (2) a hypersomnic/psychomotor retarded or catatonic psychotic episode; (3) positive family history for bipolar disorder or consecutive generation mood disorder; and (4) an episode of pharmacologically induced hypomania [60]. In general, the risk of switching is thought to be lower with SSRIs than with tricyclic antidepressants.

Pharmacokinetic interactions between antidepressants and antiepileptic drugs

Carbamazepine, phenytoin, primidone and barbiturates are potent inducers of the cytochrome P450 (CYP) enzymes at regular doses, as are oxcarbazepine and topiramate at higher doses [9]. Several of these enzymes are involved in the metabolism of tricyclic antidepressants and all SSRIs and SNRIs. The drugs affected include amitriptyline, nortriptyline, doxepine, clomipramine, mianserin, nomifensine, bupropion and, to a lesser extent, citalopram and paroxetine. The doses of these antidepressants will often need to be increased when used alongside these agents. The newer AEDs (e.g. gabapentin, lamotrigine, tiagabine, levetiracetam and zonisamide) do not have this effect [9].

Valproate is a broad-spectrum inhibitor of drug metabolism and has been associated with a 50–60% elevation in plasma amitriptyline and nortriptyline concentrations. Valproate also increases concentrations of clomipramine and paroxetine. Certain SSRIs also inhibit CYP enzymes: fluoxetine and fluvoxamine are mild to moderate inhibitors of CYP 3A4, the primary enzyme involved in carbamazepine metabolism. Neither paroxetine nor

sertraline affects plasma concentrations of carbamazepine or phenytoin, but sertraline doses of between 25 and 100 mg have been associated with both valproate and lamotrigine toxicity. There are several reports of plasma phenytoin concentrations increasing to toxic levels after initiation with fluoxetine, probably due to CYP 2C9 inhibition [61]. Phenytoin levels can also rise with co-medication with trazodone, viloxazine and imipramine. Evidence for interaction is often conflicting, and doses may need adjustment depending on levels. Citalopram, mirtazepine and venlafaxine have the least impact on CYP enzyme [9].

Pharmacodynamic interactions

The following points relate to the pharmacodynamic effects of antidepressant medication as used in general psychiatric practice (i.e. in patients without epilepsy). Whilst these findings are not specific to patients with epilepsy, the same general principles are felt to apply. On initiation of therapy with antidepressant drugs, common symptoms include a temporary worsening of anxiety and agitation, which usually passes after the first week or two. In very anxious patients, low-dose short-term benzodiazepine cover (e.g. diazepam 2 mg three times a day) may be given, and normal starting doses may be halved. Gastrointestinal symptoms such as abdominal cramps, nausea and diarrhoea are also seen. Hypertension should be examined for in patients taking venlafaxine, particularly at higher doses, and this medication should be avoided in patients at risk of cardiac arrhythmia. A variety of sexual disturbances may occur and should be asked about, as they reduce compliance. Hyponatraemia can occur with most SSRIs and is often seen in the older patient group. Co-medication with oxcarbazepine, carbamazepine or diuretics will exacerbate this. Mirtazepine is less likely to cause hyponatraemia, or sexual side-effects, but often causes sedation and weight gain. The SSRIs and SNRI venlafaxine should be taken in the morning as evening use can lead to initial insomnia. Fluoxetine is often said to have an 'activating' effect and may be useful in fatigued or lethargic patients, and those with psychomotor retardation. It also has the added benefit of being one of the few antidepressants that does not cause significant weight gain, a particular problem in patients taking AEDs that also induce weight gain, such as valproate, gabapentin and pregabalin. In the UK it is the only antidepressant currently licensed for use in children and adolescents under 18 years of age. Its other benefit is that the main active metabolite, norfluoxetine, has a half-life of 4–16 days, and in patients who regularly forget to take their medication this can often help to prevent SSRI discontinuation symptoms emerging. The latter are an effect common to all SSRIs, and symptoms include headache, rebound insomnia, increased anxiety, flu-like symptoms and electric shock-like sensations. These can best be avoided by gradual dose reduction rather than precipitate discontinuation. All patients started on SSRIs should also be warned of the possibility of an increase in suicidal thoughts and behaviours following drug initiation, and this should be asked about in the subsequent review.

Antidepressant trials in epilepsy

In view of the specific issues relating to depression in epilepsy, there is a clear need for well-conducted, controlled studies, but few such studies have been carried out. In one of the few published controlled studies, Robertson and Trimble [62] randomized 42 patients with epilepsy and depression to amitriptyline 75 mg, nomifensine or placebo. After 6 weeks, there were no between-group differences, perhaps because of the low dosages. On follow-up, 26 non-responders were openly treated with higher doses (150 mg/day) and, after a further 6 weeks, 17 patients entered remission from their depressive symptoms. Specchio *et al*. [58], in an open-label uncontrolled study, were able to show a marked improvement in depression in 39 patients treated with citalopram 20 mg/day. Kuhn *et al*. [63] analysed *post hoc* data from 2 years of treatment of 75 inpatients with major depression and TLE. They compared citalopram, mirtazepine and reboxetine, finding these drugs equally efficacious. There were no serious adverse events or drug interactions.

There are no controlled data available on the treatment of DLDE. In one open trial, however, complete symptom remission was achieved in 57% of patients treated with sertraline [24]. The mechanism of action of antidepressants in DLDE probably differs from that in other depressive disorders; the drugs are rapidly effective at low doses and are effective for anxiety, fears, irritability, insomnia, anergia, atypical pains, low mood and euphoric mood.

A practical protocol for the treatment of depression in epilepsy

There is a Cochrane review regarding antidepressants in epilepsy, but this is currently at the protocol stage, and the best current advice can be taken from the guidelines for the use of antidepressants in non-epileptic patients, with some modifications taking into account considerations mentioned above.

The largest clinical antidepressant trial to date, the National Institute of Mental Health (NIMH) STAR-D (sequenced treatment alternatives to relieve depression) trial [64], was recently completed. The trial protocol consisted of patients sequentially moving through four treatment levels depending on whether or not they responded to a particular antidepressant or combination of antidepressants. The purpose of the trial was to determine the effectiveness of different treatments for people with major depressive disorder who did not respond to the initial antidepressant treatment choice.

In treatment level 1, all patients received citalopram. One-third entered remission and a further 10–15% showed a clinically significant response. Those who did not respond were switched to treatment level 2, in which the citalopram was either (a) changed to sertraline, venlafaxine or cognitive behavioural therapy (CBT) or (b) augmented with buspirone or bupropion (both contraindicated in epilepsy) or CBT. Twenty-five per cent of the patients treated within level 2 eventually became symptom free. Level 3 treatment included mirtazepine or nortriptyline, and, in level 4, antidepressant drug combinations, such as mirtazepine plus venlafaxine, were used.

Whilst this trial was not carried out in patients with epilepsy (in whom bupropion is contraindicated and nortriptyline best avoided), a simple and evidence-based pathway for the treatment of depression in epilepsy (based on the other factors discussed above) would be to start treatment with citalopram, and then if remission of symptoms is not achieved progress through sertraline, mirtazepine and venlafaxine. Recommended starting doses, usual treatment dose and maximum doses as observed in routine psychiatric practice are outlined in Table 21.1.

Table 21.1 Commonly used antidepressants and antipsychotics: doses, receptor binding and other effects.

Antidepressant/ antipsychotic	Starting dose/timing	Usual treatment dose	Maximum dose	Pharmacology	Adverse/other effects
Citalopram	10–20 mg, morning (use 10 mg if very anxious ± panic)	20–40 mg	60 mg	H_1, inhibits CYP 2D6	Inconsistent effect at lower doses Effective in the elderly
Sertraline	50 mg, morning	50–100 mg	200 mg	SRI, DRI, sigma 1 binding	Good for atypical/psychotic (delusional) depression
Fluoxetine	20 mg morning	20–40 mg	60 mg	SRI, NRI, $5HT_{2C}$ antagonist. Inhibits CYP 2D6/3A4	Energizing and fatigue-reducing effect
Mirtazepine	15 mg, night	30 mg	45 mg	α_2, H_1, $5HT_{3/2A/2C}$	No significant sexual dysfunction Weight gain Sleep restoring Less nausea/gastrointestinal problems Anxiolytic
Venlafaxine XL	75 mg, morning	150 mg	225 mg	SRI, NRI	Extended-release version reduces side-effects, particularly nausea May be linked to more robust and longer remission rates Metabolized by CYP 2D6
Risperidone	2 mg	4–6 mg	16 mg (doses >8 mg are rarely used)	$5HT_{2A}$, D_2, α_1, α_2, $5HT_7$	EPSE at higher doses, hyperprolactinaemia, hypertriglyceridaemia, insulin resistance, HONK Less weight gain than olanzapine and clozapine Higher doses may be required due to enzyme induction by carbamazepine/phenytoin (CYP 3A4)
Olanzapine	5 mg	5–15 mg	20 mg	mACh, $5HT_{2A}$, $D_{1–4}$, $\alpha_{1/2}$, H_1, $5HT_{3/6}$, 5HT-C	Weight gain, sedation (less than clozapine) Poses definite cardiometabolic, dyslipidaemia and diabetes risks EPSEs not common Enzyme induction possible with carbamazepine (CYP 1A2)
Quetiapine	25–100 mg (depending on age)	400–600 mg	750–800 mg	D_2, $5HT_{2A/1A/2C}$, H_1, α_1, α_2, M_1	Virtually no EPSE No hyperprolactinaemia Sedation Intermediate to high risk of dyslipidaemia/insulin resistance
Amisulpiride	200 mg	400–800 mg	1200 mg	D_3. Possible D_2 partial agonist	Low EPS May cause dose-dependent QTc prolongation Can increase prolactin
Clozapine	12.5 mg	300–700 mg (adjusted according to plasma level and response)	900 mg	$D_{1–4}$, $5HT_{2A/C}$, α1/2, H,1 mACh, $5HT_{3/6/7}$	Weight gain, sedation, hypersalivation, constipation, bowel obstruction, agranulocytosis, myocarditis, seizures Sudden hyperosmolar syndrome/diabetic ketoacidosis High cardiometabolic risk Reduces suicide risk Cannot be combined with carbamazepine or lamotrigine because of risk of agranulocytosis Needs slow introduction with EEG monitoring Specialist monitoring registration

CYP, cytochrome P450; EPSE, extrapyramidal side-effects; HONK, hyperosmotic non-ketotic acidosis.

Cognitive behavioural therapy

It is likely that affective disorders respond better to a combination of pharmacotherapy and psychological therapy than to either modality alone. CBT usually involves 12–16 sessions with a specially trained psychologist or psychiatrist, during which patients' unhelpful beliefs about themselves and the world they interact with are explored. The behaviours which result from these beliefs act to reinforce the depressed state. In the therapy these views are challenged, alternative possibilities explored and a more helpful set of attitudes and beliefs encouraged.

Electroconvulsive therapy

Epilepsy is not a contraindication to electroconvulsive therapy (ECT), and in fact there is good evidence that ECT actually increases

seizure threshold. However, the use of ECT has declined significantly in routine clinical psychiatric practice but it is still employed (albeit rarely) in patients with severe depression, treatment-resistant mania and, on a very occasional basis, in psychosis.

Deep brain stimulation for treatment-resistant depression

Up to 20% of patients with epilepsy and depression fail to respond to pharmacological or psychotherapeutic interventions and may then require a trial of ECT. Despite this, some patients remain severely depressed. Several studies have demonstrated consistent involvement of the subgenual cingulate (BA25) as an area metabolically overactive in treatment-resistant depression whilst a decrease in BA25 activity has been associated with clinical response to antidepressant treatments. Mayberg *et al.* [65] tested the hypothesis that chronic stimulation to modulate Cg25 (subgenual cingulate) grey matter and interconnected frontal and subcortical regions could reverse this pathological metabolic overactivity and produce clinical benefits in patients with treatment-resistant depression. The regional cerebral blood flow (CBF) changes [using positron emission tomography (PET)] in these treatment-resistant depression patients can be seen at baseline and after 3 and 6 months of continuous deep brain stimulation (Plate 21.1). Whether these approaches would be beneficial in epilepsy and depression has not been demonstrated.

FDA guidance on suicide risk associated with antiepileptic drugs

On 31 January 2008, the US Food and Drug Administration (FDA) issued an alert regarding suicide risk in patients taking antiepileptic drugs. This warning derives from the fact that in March 2005 the FDA sent letters to sponsors of antiepileptic drugs requesting that they submit data from placebo-controlled trials for the FDA to review the possible association of suicidality events and antiepileptic drugs. In all, 199 placebo-controlled trials with a total of 27 863 patients in the drug arms and 16 029 patients in the placebo arms were submitted. Only one-third of these trials were included in the main analysis because trials without reports of suicidality were excluded [66].

The primary endpoint of the study was suicidal behaviour and ideation and this included (1) completed suicide, (2) suicide attempt, (3) preparatory acts towards imminent suicidal behaviour and (4) suicidal ideation. The secondary endpoints were (a) suicidal behaviour (completed suicide, suicide attempt, preparatory acts) and (b) suicidal ideation (suicidal ideation only). The results can be seen in Table 21.2.

There were four completed suicides in the treatment group, a rate of about 1 in 7000. Suicidal behaviour or ideation occurred in 1 in 270 of the drug-treated group compared with 1 in 416 of the placebo group. The overall number needed to harm was 2 per 1000 and the odds ratio was significant at 1.8. In subanalyses for each individual drug, carbamazepine and valproate appeared to reduce suicidal behaviour and ideation events, although this effect was not significant; nevertheless, the alert currently includes the entire class of antiepileptic drugs. In November 2007, the sponsor of lamotrigine submitted three additional placebo-controlled trials, which were not part of the primary analysis. In these three trials there were nine suicidal behaviour or ideation events, only one of which occurred in the drug arm, with the other eight occurring in the placebo arm. The overall odds ratio decreased to 1.55 but remained significant (1.09–2.21). The alert raises significant concerns that patients might stop their antiepileptic drugs, placing them at higher risk of accidental injury and sudden unexpected death in epilepsy (SUDEP). Unfortunately, in our opinion, the points above reduce the validity of the data. Data on suicide need to be collected in a prospective and systematic way and, given the complexity of the relationship between epilepsy, depression and suicide, this meta-analysis is insufficiently robust to be of much value [66].

Table 21.2 Results from the Food and Drug Administration analysis in suicidal behaviour and ideation associated with antiepileptic drug use.

Primary endpoint: suicidal behaviour and ideation	Number	Number of completed suicides (ratio)	Suicidal behaviour or ideation (ratio)	Odds ratio
Drug arm	27 863	4 (1/6966)	0.37% (1/270)	1.8 (1.24–2.66)[a]
Placebo arm	16 029	0	0.24% (1/416)	
Secondary endpoints				
Suicidal behaviour	–	–	–	2.92 [1.44–6.47]
Suicidal ideation	–	–	–	1.45 [0.93–2.30]

[a] Odds ratio prior to additional lamotrigine data.

The psychoses of epilepsy

The psychoses of epilepsy have been the subject of considerable research over the past century. Much of this has been carried out by psychiatrists, whose approach has been to examine these phenomena through the empirical prism of descriptive psychopathology (i.e. without reference to causality) in order to determine to what extent the psychoses of epilepsy are similar to, or differ from, those seen in the 'functional psychoses'. The approach often taken by neurologists has been more biological, linking the symptoms to electrophysiological activity or seizure occurrence. The 'gold standard' investigation of this approach is intracranial stereo-EEG.

There are also strikingly divergent views regarding the causation of affective and psychotic states in patients with epilepsy. Some have emphasized an apparent biological antagonism between affective/psychotic symptoms and ongoing seizures, as described below in the section on forced normalization and which incidentally led von Meduna to introduce iatrogenic convulsions to treat schizophrenia. Others, for instance Slater, postulate a positive link between epilepsy and schizophrenia, an observation elaborated upon subsequently by findings from SEEG. This is a very complex area. One clinical approach has been to subdivide these disorders into ictal, postictal and interictal types, even if at the electrophysiological level these distinctions are less clear. Furthermore, some psychosis in epilepsy may be due to ongoing non-convulsive complex partial (limbic) status epilepticus, some is AED related and some may reflect other changes in neurophysiological activity.

Ictal psychosis (complex partial status epilepticus)

Complex partial status epilepticus is an epileptic condition which provides one of the clearest examples of the propensity of epilepsy to cause prolonged or persisting hallucinatory states. A detailed exploration of this area is beyond the scope of this chapter; however, the reader is referred to a detailed review of the available SEEG data correlating psychotic symptoms with limbic epileptic discharges [67,68]. Psychiatric features include inaccessibility, delusions, illusions, visual or auditory hallucinations, ideas of reference, paranoia, thought disorder and often a rather curious but characteristic perseverative obsessive insistence on oppositions (such as black/white, good/bad, right/left). The hallucinatory experiences often have religious content. The attacks typically last hours, but can be much more prolonged (occasionally continuing for months or years). The attacks are usually self-limiting, and the symptoms frequently fluctuate or 'cycle' [69].

Postictal psychosis

The concept of postictal psychosis can be dated back to the work of Jackson [70] on 'temporary mental disorders after epileptic paroxysms'. Despite this, and the fact that it is the most frequent psychotic condition seen in patients with epilepsy, it did not become the focus of attention until more recently [71,72]. There continues to be no universally agreed definition, although that used by Kanemoto *et al.* [73], including any psychotic episode occurring within 7 days of the last generalized tonic–clonic seizure or cluster of complex partial seizures, is useful.

Common findings among the different case series include (1) delay between the onset of psychiatric symptoms and the time of last seizure; (2) relatively short duration of psychosis; (3) affect-laden symptomatology; (4) the clustering of symptoms into delusional and affective-like psychoses; (5) an increase in the frequency of secondary generalized tonic–clonic seizures preceding the onset of postictal psychosis; (6) the onset of postictal psychosis after a long duration of epilepsy (for a mean period of more than 10 years); and (7) a prompt response to low-dose antipsychotics or benzodiazepines [74].

The phenomenology of postictal psychosis has also been extensively addressed. Most episodes occur in patients between 30 and 40 years of age, and in 86% they follow a clear increase in generalized seizure frequency. The lucid interval can last between 1 and 6 days (mean 2.5) in 75%, following which hallucinations (mainly auditory) are found in about one-third and delusions (mainly persecutory) in one-quarter. One study found that patients fulfilled present state examination (PSE) criteria for schizophrenic psychosis in four, manic/mixed affective psychoses in three and paranoid psychoses in four. They found the psychopathology to be identical to that found in the functional psychoses. Mood was markedly abnormal (elevated, depressed or both) in three-quarters, one-half had paranoid delusions and both auditory and visual hallucinations were common. Hypomania and religiosity following temporal lobe seizures has also been noted and patients appear more likely to experience grandiose and religious delusions in the presence of elevated mood and a feeling of mystic fusion of the body with the universe [68,75].

The other interesting point to raise is that it is likely that at least some cases of apparently 'postictal psychosis' are not in fact 'postictal' at all but are due to ongoing seizure activity – and thus can be categorized as cases of non-convulsive status epilepticus [67,68,76,77]. This has led Oshima *et al.* [78] to suggest that postictal psychosis should be subdivided into two types: first, a nuclear type representing the established clinical picture as described by Kanner above and occurring as an indirect after-effect of seizure activity and, second, an atypical peri-ictal type, occurring as a direct manifestation of limbic epileptic discharges (i.e. complex partial status).

The interictal psychosis of epilepsy

Definition

As Sachdev [79] has pointed out in his review on epileptic psychoses, most studies have lacked a precise definition of either 'psychosis' or 'epilepsy'. Definitions for interictal psychosis need to exclude peri-ictal psychosis, allow for the subcategories of drug induced and the possibility of 'alternative' psychosis, and be present in the absence of seizure discharges. They are frequent and clinically more significant than the peri-ictal psychoses in terms of severity and duration.

Prevalence

There is a great deal of variance in prevalence estimates for psychosis in epilepsy. Reported prevalence rates range from 4.3% and 6% in IGE and TLE groups, respectively [80], to 40.2% and 44% for those with 'centrencephalic' epilepsy and 'psychomotor' epilepsy, respectively [81]. In a later review by Sengoku *et al.* [82], more intermediate rates (19.4% and 15.2% in the IGE and TLE groups, respectively) were reported, and these correspond well with recent work by Filho *et al.* [83], who reported psychotic disorders in 15.8% of 85 patients with TLE plus mesial temporal sclerosis.

Relationship to epilepsy subtype

Throughout the twentieth centrury, there have been numerous attempts made to assign different psychiatric features to the different types of epilepsy. Several studies have not found significant differences [81], and more recent attempts to relate psychopathology to epilepsy localization have also been equivocal [84]. In one of the largest population-based studies to date, Qin *et al.* [85] found that people with a history of epilepsy were two to three times more likely to develop schizophrenia or schizophrenia-like psychosis than people who had never had epilepsy again. They did not find a difference according to the type of epilepsy.

Nevertheless, there is a strong clinical impression that patients with epilepsy involving limbic structures may be particularly vulnerable to psychotic disorders and the view that patients with TLE are particularly prone to psychosis is widely held. Stevens [86] sums up what are still contemporary views: 'It would be correct to say that nearly two thirds of all the adult epileptics studied who were known to have had psychotic episodes which required hospitalisation also had a diagnosis of psychomotor temporal epilepsy.'

Psychopathology in interictal psychosis: comparison with primary psychoses

In the 1950s, Hill and Pond observed that whilst patients with psychosis in epilepsy could experience positive symptoms

(delusions and hallucinations), they tended to remain 'warm and appropriate' and the course of illness lacked the usual deterioration of personality seen in schizophrenia [87]. Slater *et al*. [88] agreed but added that 'the delusions and hallucinations of patients with the psychosis of epilepsy are empathiseable' (i.e. the patient remains in our world). Other key features are the absence of negative symptoms and better premorbid function [88,89]. Interictal manic or bipolar presentations are considered rare. Notable exceptions include Flor-Henry's [90] series, in which an affective psychosis occurred in 40% of patients, and the prevalence rate of 70% for depressive psychosis reported by Fenton [91].

By way of contrast, Mendez *et al*. [92] found that 'the schizophrenia of epilepsy appears to conform to the usual schizophrenic categories' and Perez and Trimble [89] found that 46% of their epilepsy group had nuclear schizophrenia symptoms almost indistinguishable from those seen in patients with schizophrenia.

To summarize, it would seem that the key differences lie in a preservation of affect, fewer negative symptoms and arguably greater insight, whilst the greatest similarities can be seen in positive symptomatology (i.e. that of thought disorder, delusions and hallucinations). Nevertheless, these differences have not been consistently found, and the similarities of the two conditions are much greater than any differences. An interesting point about the interictal psychosis of epilepsy is that it develops almost always only after the epilepsy has been present for many years (usually after a decade or so of seizures) and almost always in patients in whom epilepsy control has been poor.

Forced normalization

Chronic interictal psychoses also seems to be more common than at the beginning of the last century [9]. One explanation advanced for this phenomenon is that it arises as an undesirable result of modern AEDs suppressing epileptic or neurophysiological activity. It has been suggested that the epileptic and psychiatric components of psychomotor epilepsy might be physiologically antithetical [93,94].

'Forced normalization' is a term coined by Landolt [95], who noted that in occasional patients the electroencephalogram (EEG) became 'normalized' each time the patient's mood became dysphoric, and there appeared to be an alternating pattern of interictal psychosis and seizures. This led Landolt to define forced normalization as 'the phenomenon characterized by the fact that, with the recurrence of psychotic states, the EEG becomes more normal, or entirely normal, as compared with previous and subsequent EEG findings' [96]. More recently, the concept has been loosened to refer to almost any psychiatric disorder occurring in patients whose seizure frequency is reduced (disregarding the EEG altogether), and elaborate explanatory theories have been derived from doubtful evidence. One criticism of the original concept, and particularly of the loose extrapolation to include seizures as well as EEG change, is that the reverse situation is much more commonly observed in clinical practice – where psychotic behaviour is increased at times of seizure exacerbation or worsening EEG change. In the eyes of most epileptologists, the concept of forced normalization is of dubious validity and little practical importance, except perhaps in very occasional circumstances. Furthermore, the scalp EEG is a notoriously insensitive tool at detecting epileptic activity in medial limbic structures and a normal scalp EEG is by no means a reliable predictor of quiescent epilepsy.

Psychosis and temporal lobe surgery

When temporal lobectomy was first introduced in the 1950s, it had been hoped that it would alleviate the psychosis of epilepsy as well as seizures; indeed, psychosis was seen as a positive indication. However, it was rapidly recognized that temporal lobectomy also often made psychosis worse. The literature in this area is extensive but the main themes are as follows: some patients can be cured of their psychosis following surgery (although relapse is probably common) [97,98]; more commonly, however, the psychosis can be exacerbated by surgery [99]; and *de novo* psychosis can also occur after epilepsy surgery – in perhaps 5% or more of cases [98–101]. Matsuura [102] found *de novo* interictal psychosis in about 4% of cases, and in two-thirds complete seizure remission following surgery had not been achieved, In two of Shaw's series [101] there was a close temporal link between the recurrence of seizures postoperatively and the first appearance of psychotic symptoms. One of the significant risk factors included bilateral preoperative EEG abnormalities. Right-sided resections appear to be associated with an increased vulnerability to developing psychosis postoperatively [100,102,103]. The data are not entirely consistent, however, and it is clear also that psychosis can follow both left- and right-sided operations [68].

Therapy of psychosis in epilepsy

Pre-ictal, ictal and postictal hallucinations are best treated by controlling the ictus, and thus by AEDs. In cases where postictal psychosis is thought to be due to ongoing limbic status epilepticus, acute therapy with benzodiazepines is usually advised, sometimes with additional antipsychotic therapy (see below) if the psychosis is florid. Clobazam is a common AED choice given orally at 20–30 mg/day over several days. The postictal psychosis of epilepsy has also been shown clearly to respond to ECT [104], although it is hardly ever necessary to resort to this in current practice. It is important to ensure that patients are nursed with the appropriate level of supervision in a contained environment and protected from causing harm to themselves or others.

In patients with chronic interictal psychosis, antipsychotic drug therapy is needed in most cases. In general, modern atypical antipsychotic drugs, such as risperidone, olanzapine, amisulpiride, sulpiride and quetiapine, in relatively low doses, are sufficient to control symptoms, although on occasion combinations of antipsychotic drugs (e.g. amisulpiride and olanzapine) or clozapine may be required in particularly treatment-resistant cases. Recommended starting doses, usual treatment dose and maximum doses as observed in routine psychiatric practice are outlined in Table 21.1.

Treatment is complicated by the fact that almost all available antipsychotics are mildly epileptogenic, with seizure incidence rates (in patients who previously had not had seizures) ranging from approximately 0.1% to approximately 1.5% (the incidence of the first unprovoked seizure in the general population is 0.07 to 0.09) [105]. EEG changes seem to occur in about 7% of patients treated with antipsychotic drugs, but in most cases are of little clinical consequence [106]. In one recent review, seizure incidence for the different atypical antipsychotics was given as

0.3% for risperidone and 0.9% for olanzapine and quetiapine. Another study found that a set of all antipsychotics (olanzapine, quetiapine, clozapine, risperidone, ziprasidone and aripiprazole) was not significantly associated with an increased risk of seizures after the removal of both olanzapine and clozapine from the group [54]. The risk with clozapine increased in a dose-dependent manner from 1.0% with low doses (<300 mg/day) to 2.7% with moderate doses and 4.4% with high-dose (600–900 mg/day) treatment [107]. Pacia and Devinski [108], in a postmarketing study of more than 5000 patients on clozapine, showed a lower rate (1.3%) with no dose dependency, and when Langosch and Trimble [109] treated six patients with epilepsy and severe psychosis with clozapine, none showed an increase and in three there was a substantial reduction in seizure frequency.

The fear of eliciting additional seizures has led to an exaggerated sense of caution in antipsychotic drug use. In patients comedicated with AEDs (as is almost always the case in patients with epilepsy and psychosis) the risk of an increase in seizures is low. However, this risk can be a particular issue for those who are seizure free, in whom the recurrence of seizures has a generally greater impact.

Further problems associated with antipsychotic drug treatment in patients with epilepsy include (a) variation in the individually inherited seizure threshold (for a thorough review see ref. 90); (b) side-effects, in particular sedation, weight gain, worsening of glycaemic control, haematotoxicity and hepatotoxicity, some of which can be moderated by careful dose titration; and (c) a relative lack of studies investigating the efficacy of antipsychotic drugs in the psychoses of epilepsy (a 2006 Cochrane review protocol of this area was able to identify only one randomized controlled trial that met their inclusion criteria). In addition, pharmacokinetic interactions may result from common metabolism via CYP isoenzymes. Carbamazepine and other enzyme-inducing AEDs lower concentrations of haloperidol, chlorpromazine, clozapine, olanzapine, risperidone and quetiapine. These interactions can be very marked (by to 50% on occasions) and clinically important. Valproate has few interactions, and the antipsychotics do not generally affect AED concentrations.

Personality and organic mental disorders

The personality changes of epilepsy have been examined, broadly speaking, in three different ways: (1) the epileptic personality; (2) DSM-IV Axis-II personality disorders; and (3) the organic mental disorders (OMDs) described by the Lindqvist and Malmgren scheme.

The epileptic personality

The first psychoanalytic theorists focused on the 'epileptic personality', which was said to comprise such features as impulsivity, egocentricity and affective viscosity. Later, neurologists such as Gastaut *et al*. [110] confirmed these observations, recorded hyposexuality, hypoactivity and aggressiveness in addition, and noted that this stereotypic symptom complex was the antithesis of the behaviours seen in the Kluver–Bucy syndrome. Waxman and Geschwind [111] later coined the term 'interictal behaviour syndrome' (also known as the 'Gastaut–Geschwind syndrome) to describe a distinct subset of behaviours associated with TLE. These included:

1 viscosity – defined as the tendency to prolong interpersonal encounters, and often associated with circumstantial and pedantic speech;
2 religiosity – there is some evidence that patients with TLE, in particular, experience this personality trait, and differ from patients with extratemporal epilepsies or controls in this regard and sudden religious conversions associated with increased seizure activity have also been reported [112,113];
3 hypergraphia – a tendency towards extensive and sometimes compulsive writing with a striking preoccupation for detail;
4 hyposexuality, including decreased libido and impotence in about half of TLE patients without gender bias [112], although Fenwick *et al*. [114] did not find any significant difference in hyposexuality related to type of epilepsy or seizure frequency; and
5 aggression.

The Kluver–Bucy syndrome occurs as a consequence of bilateral anterior temporal destructive lesions and comprises oral exploratory behaviour, hypersexuality and decreased aggression. It may be seen in patients with TLE who have had a unilateral temporal lobectomy and who then suffer compromise of the contralateral temporal lobe due to a brain injury, cerebrovascular disease or other pathology.

DSM-IV Axis-II personality disorders

The general diagnostic criteria for a personality disorder, according to DSM-IV, specify an 'enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture'. This may be manifested as follows: (1) in the patient's way of seeing him/herself, other people or events; (2) the range, intensity, lability and appropriateness of affectivity; (3) impulse control; and (4) interpersonal functioning. These patterns should be enduring, inflexible and pervasive across a broad range of personal and social situations, lead to significant distress or impairment of function, be stable and of long duration, and should not occur secondary to another mental disorder or to the effects of drug use or a general medical condition.

In patients with epilepsy, the prevalence of Axis-II personality disorders ranges from 18% to 61% across studies, with a mean of 31% [112]. Koch-Stoecker [115] found that, of 100 patients who underwent anterior temporal lobectomy, 14% were subsequently hospitalized for psychiatric complications postoperatively, all of whom exhibited a preoperative Axis-II disorder. None of their patients with only an Axis-I disorder were hospitalized. Derry *et al*. [116] found that patients high in preoperative (anterior temporal lobectomy) neuroticism exhibited significantly worse postoperative psychosocial adjustment and quality of life.

The 'organic mental disorders' (OMD) of Lindqvist and Malmgren

The OMD classification of Lindqvist and Malmgren (the LM scheme) is one of the least studied and least well known of the current classification systems of psychiatric disorder in epilepsy. This is due, in part, to the fact that the concept was originally

detailed in a book published in Swedish in 1991 and there has been only one related article in English [117]. Nevertheless, the syndromes described 'ring true' to many neurologists working with patients who have epilepsy, and it is worth reviewing here.

The LM scheme is the result of the collaboration of a psychiatrist (Göran Lindqvist) and a philosopher/physician (Helge Malmgren). It was developed in Sweden in the early 1990s, and is principally based on the personal experience of the two authors and organized according to logical and semantic considerations [117,118]. The authors base the postulate of their classification upon the existence of a 'level between observable symptoms and distal aetiology' and argue that this level might explain the variety and complexity of mental disorders which occur secondary to somatic disease. As little is known about the processes that link somatic aetiologies and mental symptoms, they can only be introduced as theories, hence the term 'hypothetical pathogenetic processes' (HPPs) [117]. Accordingly, the authors divide OMDs into six basic categories: (1) astheno-emotional disorder (AED); (2) emotional–motivational blunting disorder (EMD); (3) somnolence–sopor–coma disorder (SSCD); (4) confusional disorder (CD); (5) hallucination–coenestopathy–depersonalization disorder (HCDD); and (6) Korsakoff's amnestic disorder (KAD). The typical clinical manifestation, course and main aetiologies of each are summarized in Table 21.3.

Each disorder can occur separately or together with one or more other OMD, and all six disorders may be seen in epilepsy. However, three are more specific to this disorder: the astheno-emotional disorder, the EMD and the HCDD [117,119]. The number of studies using the LM scheme in the assessment of OMD in patients with intractable epilepsy is, unfortunately, small, and the study conducted by Malmgren in 2002 remains the best example of the usefulness and efficacy of this classification [119]. In this study, Malmgren followed up, both pre- and postoperatively, a series of 70 patients: 54 underwent temporal and 16 underwent extratemporal resections. When presurgical evaluation was carried out on all patients, 38.6% of patients were reported to have an OMD, of which astheno-emotional disorder (22.9%) and EMD (15.7%) were the most common. Postoperatively, 60.9% of patients showed an OMD at some time, the most common diagnosis again being the astheno-emotional disorder in both temporal and extratemporal lobe resections (49.1% and 50%, respectively). The frequency of EMD was significantly higher in the extratemporal resection group (37.5% compared with 9.4% in patients with temporal lobe resections). The correlation between pre- and post-surgical psychiatric morbidity was also analysed. Patients with preoperative anxiety–depressive disorders (ADs) as well as pre- and/or post-surgical astheno-emotional disorder were significantly more likely to develop an AD postoperatively than patients with no such history. This risk was also reported to be higher for patients with

Table 21.3 The organic mental disorders [123].

OMDs	Typical manifestations	Course	Causes	Equivalents	
				DSM-III or DSM-III-R	ICD-10
AED	Primary symptoms: *Mild to moderate forms:* Concentration difficulties (specifically problems with upholding sustained attention) Mental fatigability Secondary memory disturbances (affecting short-term memory as well as storing to, and retrieval from, long-term memory) Emotional lability Irritability *Severe forms* (in addition to the above symptoms): Slowed and impoverished associations Reduced ability to apprehend complex facts Destruction of stored long-term memory traces Psychogenic, secondary symptoms Lowered self-esteem Feelings of uncertainty Anxiety Depressive reactions (even severe depressions) Psychosomatic complications including headache Paranoid reactions	In organic cases, the prognosis depends both on the underlying aetiology, the degree of severity of the astheno-emotional disorder, and also on the patient's age Mild and moderately severe cases in young patients: usually heal completely when the underlying somatic aetiology is eliminated Severe cases: prognosis often unfavourable	Mild astheno-emotional disorder can be either organic or psychogenic. Moderately severe cases are usually of organic origin, and the severe forms always have an organic underlying aetiology Can be due to all kinds of localized organic brain diseases or injuries: traumatic injuries, tumours, infections, degenerative and vascular diseases	Dementia (severe, pure astheno-emotional disorder) Organic personality disorder (moderately severe forms with prominent emotional symptoms) Organic mental syndrome not otherwise specified (DSM-III-R) and atypical or mixed organic brain syndrome (DSM-III) for mild astheno-emotional disorder	Dementia Organic amnestic syndrome Organic personality disorder Organic emotionally labile [asthenic] disorder Neurasthenia Unspecified mental disorder Post-concussional syndrome Mild cognitive disorder

Table 21.3 *Continued*

OMDs	Typical manifestations	Course	Causes	Equivalents	
				DSM-III or DSM-III-R	ICD-10
EMD	Emotional shallowness: lack of feelings and consideration for other people, including family members Motivational blunting: general or restricted to particular fields such as personal hygiene or professional ambitions Alteration of cognitive function: capacity of abstraction, foresight, planning, and self-criticism Behavioural disorders: often barely noticeable, some patients may be 'extremely inactive, unspontaneous' while others are 'thoughtless, unrestrained, economically rash, promiscuous' or even show 'a criminal behaviour'	Variable according to the underlying aetiology. The EMD can progressively worsen (cerebral gliomas), be stationary without any improvement (serious brain injury), or, in the majority of cases, spontaneously heal	Usually due to frontal lobe damage, and often referred to as 'frontal lobe syndrome'. It is also described in injuries to limbic structures, thalamus and hypothalamus, as well as severe endocrinopathies	Organic personality disorders for mild, moderately severe and a number of more severe cases; dementia for severe cases	Dementia Organic personality disorder Organic emotionally labile [asthenic] disorder
SSCD	Severe forms: coma of varying depth Moderately severe forms: psychomotoric dampening with a general impairment of most cognitive, emotional and motivational performances, as well as an increased tendency to fall asleep Mild forms: slight, unspecific and usually hard-to-diagnose symptoms		May be the result of toxic influences on the brain, raised intracranial pressure or a number of clinical situations such as pituitary adenoma with suprasellar extension	Delirium Dementia (severe cases)	Dementia Delirium
CD	Pathognomonic sign: incoherence in thought and speech Other symptoms: disorientation, anxiety, hallucinations and illusions	Usually acute	Common complication of diffuse or localized mechanical or chemical brain injury Often psychogenic	Delirium for organic aetiologies Brief reactive psychosis for psychogenic cases	Dementia Delirium
HCDD	Fully blown cases: visual hallucinations or visuoperceptual disturbances, coenestopathies, and feelings of depersonalization and/or derealization. Auditory hallucinations do not occur. In most cases, only one or two symptoms mentioned above are present	Evolution usually towards spontaneous remission even if the underlying aetiology remains unchanged	Intoxications (especially with hallucinogens), migraine, endocrinological diseases, brain traumas, dysfunction of the hypothalamus and/or the temporal lobes (e.g. temporal lobe epilepsy) Psychogenic	Organic hallucinosis	Dementia Organic delusional disorder Organic hallucinosis Acute psychotic disorders
KAD	Fully developed: combination of retrograde amnesia, short-term memory impairment, disorientation and confabulation	Variable according to the underlying aetiology. Can be chronic and stationary (alcoholic dementia), subchronic and gradually healing (moderately severe post-traumatic amnesia) or transient (transient global amnesia)	Bilateral lesions, or dysfunction of the limbic system, the hypothalamus or certain parts of the thalamus	Amnestic syndrome for pure cases of KAD Dementia for patients with KAD and additional cognitive deficits	Dementia Organic amnesic syndrome

AED, astheno-emotional disorder; CD, confusional disorder; EMD, emotional–motivational blunting disorder; HCDD, hallucination–coenestopathy–depersonalization disorder; KAD, Korsakoff's amnestic disorder; SSCD, somnolence–sopor–coma disorder.

a presurgical astheno-emotional disorder than those who *de novo* developed this disorder after the surgery. Laterality or site of resection, histopathology and seizure outcome were not significantly correlated to pre- and/or post-surgical diagnoses of astheno-emotional disorder. One year after the resective surgery, the prevalence of the astheno-emotional disorder was equivalent to the preoperative degree [119].

These disorders are likely to be missed unless specifically enquired about because they are not considered separately in the two main diagnostic classification schemes (ICD-10 and DSM-IV). Although each disorder, as described by Lindqvist and Malmgren, has one or several approximate equivalents in both DSM-IV and ICD-10 (see Table 27.3), the diagnosis does not map easily across schemes. Neither DSM-IV nor ICD-10 recognizes the astheno-emotional disorder, the components of which are lost under a variety of disparate diagnoses such as neurasthenia and dementia.

Mental and behavioural disorders secondary to antiepileptic drug use

Antiepileptic drugs have been associated with numerous psychiatric adverse events (PAEs), including, for example, (1) barbiturates with depression and attention deficit–hyperactivity disorder in children; (2) phenytoin with toxic schizophreniform psychoses; (3) valproate with acute and chronic encephalopathies; (4) vigabatrin, topiramate and other drugs with depression and alternative psychoses [120]; and (5) levetiracetam with irritability, aggressivity and psychosis.

An attempt has been made to determine the risk of PAEs according to mechanisms of action of the AEDs [e.g. γ-aminobutyric acid (GABA)-ergic or antiglutamatergic] [121], but this schema can only partly explain the PAEs. Mula *et al*. [122] tested the hypothesis that some patients are generally more prone to developing psychopathology during AED therapy, irrespective of the mechanism of action of the drug. They investigated the occurrence of PAE with topiramate and levetiracetam in the same population of patients with epilepsy. They found that patients on topiramate tended to have well-defined DSM-IV clinical pictures (in particular depression associated with rapid dose titration), whereas those on levetiracetam experienced more subsyndromal behavioural changes (aggressive behaviour and emotional lability). Most interesting was the fact that a subgroup of patients appeared prone to developing PAEs regardless of the particular AED used. Significant risk factors included (1) a history of drug-resistant epilepsy; (2) febrile convulsions (suggesting that early limbic injury predisposes to psychiatric vulnerability that can be triggered by AEDs); and (3) previous and familial psychiatric history [122].

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22 Management of Side-effects of Antiepileptic Drugs

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In epilepsy treatment, the management of adverse effects of antiepileptic drugs (AEDs) is of crucial importance, requiring knowledge of risk factors and strategies for prevention and early identification. The treatment of adverse effects can require drug reduction or discontinuation and/or specific measures. All steps depend on the establishment of a therapeutic alliance with active patient involvement. After a drug is selected for use, the benefits and risks should be discussed with the patient. The nature of adverse effects should be explained and this can minimize the risk and consequences of many unwanted complications.

Antiepileptic drug-induced adverse effects may be roughly divided into two broad classes: type A (pharmacology related) and type B (idiosyncratic adverse effects). This said, some adverse effects do not fit easily into either category.

Type A adverse effects are predictable, dose dependent, usually observed at the beginning of a treatment or after a dose increase, and explained by the known pharmacological properties of individual agents [1]. These effects, which generally involve the central nervous system (CNS), are usually reversible upon dosage adjustment and rarely require discontinuation of therapy.

Type B adverse effects occur sporadically and unpredictably, and their pathogenesis is the consequence of an abnormal, often immunological, reaction [2]. These can be caused by allergic or direct cytotoxic mechanisms or may be the consequence of effects apparently unrelated to the known mechanisms of action of the offending drug. This last phenomenon is sometimes known as 'off-target pharmacology'.

The identification of adverse effects

Type A, dose-dependent adverse effects, which are relatively frequent, are generally identified during the prelicensing clinical development of a drug. However, the rates of detection are clearly influenced by the method of detection, which varies from spontaneous reporting to the use of checklists [3].

Analysis of double-blind, placebo-controlled studies may be the only way to identify a causal relationship between the experimental drug and some of the most frequently observed treatment-emergent CNS adverse effects (Table 22.1). The incidence of a particular adverse event can be estimated by subtracting the rate on the placebo arm from the rate in the active treatment arm [4].

Treatment with AEDs has also been associated with some chronic adverse effects (e.g. weight gain, reduction in bone mineral density, gingival hyperplasia, etc.) which cannot be identified in double-blind studies because of their limited duration. Long-term and observational studies are the only way to appreciate the frequency and characteristics of these complications.

The most severe type B idiosyncratic reactions occur rarely – in approximately 1 of 30 000–50 000 exposures for most AEDs [5]. Hence, information on their occurrence can only be acquired through drug surveillance programmes, such as spontaneous reports to regulatory authorities [2].

Adverse effects of antiepileptic drugs

Here, a general overview of AED tolerability will be given, and detail of individual drugs is given in the relevant chapters devoted to each specific drug. Teratogenesis is discussed in Chapter 25.

Central nervous system adverse effects

The majority of adverse effects exerted by AEDs involve the CNS. Such side-effects are relatively frequent and more commonly observed at the onset of a treatment or after a dose increase. They are usually promptly reversible after dose reduction. Some CNS adverse effects are more rarely observed and more idiosyncratic in nature.

Disturbances of vigilance and cognitive abilities

Somnolence is the most frequent adverse effect induced by traditional AEDs. It is more frequently observed in patients treated with phenobarbital or primidone than in patients treated with carbamazepine and phenytoin [6]. Somnolence is also reported during treatment with valproate [7,8].

Several new AEDs have sedative properties (see Table 22.1). Felbamate has stimulant-like properties [9]. Somnolence, which can be observed during treatment with this drug, can also be caused by inhibition of metabolism of associated AEDs.

The negative impact of antiepileptic treatment on cognitive functions is a particularly concerning effect, which may not be easily detected and can have important consequences. It has been recognized since the 1990s, for instance, that there is a drug-induced depression of cognitive performance in children treated with phenobarbital for febrile seizures, which may outlast the administration of the drug by several months [10].

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Table 22.1 Central nervous system dose-dependent adverse effects significantly associated with new antiepileptic drugs.

Antiepileptic drug	Adverse effect	Risk difference	95% confidence interval
Gabapentin	Somnolence	0.13	0.06–0.20
	Dizziness	0.11	0.07–0.15
Lamotrigine	Ataxia	0.12	0.01–0.24
	Diplopia	0.12	0.00–0.24
	Dizziness	0.11	0.05–0.17
Levetiracetam	Somnolence	0.07	0.01–0.12
Oxcarbazepine[a]	Diplopia	0.23	0.18–0.28
	Dizziness	0.20	0.14–0.27
	Somnolence	0.15	0.09–0.21
	Ataxia	0.15	0.10–0.19
	Nystagmus	0.13	0.09–0.17
	Vertigo	0.08	0.05–0.12
	Fatigue	0.07	0.02–0.12
	Tremor	0.05	0.01–0.08
Pregabalin	Dizziness	0.22	0.16–0.28
	Somnolence	0.11	0.07–0.15
	Ataxia	0.10	0.06–0.14
	Fatigue	0.04	0.01–0.08
Tiagabine[a]	Dizziness	0.18	0.06–0.30
	Cognitive impairment	0.06	0.01–0.12
Topiramate	Cognitive disturbances	0.14	0.06–0.22
	Somnolence	0.09	0.04–0.14
	Dizziness	0.06	0.00–0.11
	Fatigue	0.06	0.01–0.12
Zonisamide	Somnolence	0.06	0.02–0.11
	Dizziness	0.06	0.00–0.12

From ref. 4.

All adverse effects which were found to be significantly associated with the experimental AED are reported in the table above. Meta-analysis of all double-blind, placebo-controlled studies performed in adults. Risk difference was calculated using the random effect model. Due to heterogeneity of analysed studies, no comparisons between AEDs are possible.

[a] No meta-analysis was performed for oxcarbazepine and tiagabine and risk differences (95% confidence interval) were calculated for each drug from only one study in each case.

Studies performed with traditional AEDs show that many AEDs can cause negative cognitive effects, when compared with no treatment in cross-over studies conducted in healthy volunteers. The effect of phenytoin, carbamazepine and valproate is relatively small and there is little difference between the three drugs. However, phenobarbital, and also other drugs used in polypharmacy, have been shown to have a greater negative impact on cognition [11].

In general, the newer AEDs exhibit only weak effects on cognition. Topiramate is an exception, and this drug carries the risk of a significant negative effect on attention and also a specific effect on verbal function and language [11].

Disturbances of brainstem and vestibulocerebellar system

Many drugs cause brainstem and/or cerebellar dysfunction. This causes subjective and objective disorders of balance and gait (ataxia, incoordination, dizziness and vertigo) and disturbances of the oculomotor system (diplopia, oscillopsia and nystagmus).

Ataxia and nystagmus are typical manifestations of acute phenytoin and carbamazepine toxicity, and are usually dose related [12]. Although both phenytoin and carbamazepine can produce cerebellar and brainstem dysfunction, there are clinically relevant differences in the drug effects. Carbamazepine usually causes intermittent diplopia and ataxia [12] correlated with fluctuations of serum drug concentrations. Phenytoin-induced ataxia is not intermittent and insidiously and progressively worsens, sometimes over months. The phenytoin-induced ataxia is usually reversible and dose related [12], but can sometimes persist after drug withdrawal. Purkinje cell degeneration and astrocytic changes have been observed in patients who had prolonged intoxication with this drug [13].

Barbiturates, and in particular phenobarbital, seem to have a different spectrum of neurotoxicity, with sedation usually appearing as the first symptom [12]. Among traditional AEDs, sodium valproate is considered to have the least effects on vestibulocerebellar structures [8].

Among the newer AEDs, ataxia is significantly associated mainly with lamotrigine, oxcarbazepine and pregabalin therapy (see Table 22.1).

Disturbances of basal ganglia and other motor central nervous system structures

Antiepileptic drugs are also associated with other motor adverse effects. These can be dose-dependent effects or can have an idiosyncratic nature, being unpredictable and with a rare occurrence at low dosages [2].

Tremor is frequently observed during treatment with valproate [14]. The co-medication of lamotrigine and valproate seems to worsen this adverse effect. Tremor may also be induced by tiagabine [15].

Valproate can also cause a reversible parkinsonian syndrome, which usually appears a few days after the beginning of a treatment with the drug [8]. This syndrome may also have an insidious onset and become clearly detectable only after many years.

Several cases are reported in the literature [16] of dyskinesias induced by phenytoin. Choreoathetosis is the most common manifestation and orofacial dyskinesia, dystonia and ballism are less frequent. Sporadic cases have also been signalled of dyskinesias during treatment with several other AEDs [12].

Tics have been sporadically described during carbamazepine and lamotrigine treatment and, exceptionally, during treatment with phenobarbital and phenytoin [12].

Non-epileptic myoclonus may appear in the course of valproate encephalopathy [17], and can be caused by some new AEDs such as gabapentin and pregabalin, mainly in patients with brain damage [18].

Encephalopathies

Encephalopathies can be observed during intoxication with several AEDs. High phenytoin blood levels, for instance, can

result in ataxia, nystagmus, mental slowing to the level of stupor and coma, and an increase of seizure frequency [12].

Valproate-induced toxic encephalopathy is an example of an idiosyncratic CNS reaction. This is characterized by disturbances of consciousness ranging from a confusional state up to stupor and coma, asterixis and EEG slowing [17]. Exceptional cases of a vigabatrin-induced encephalopathy with stupor, confusion and EEG slowing have been described [19]. A hyponatraemic encephalopathy characterized by mental changes up to coma and EEG slowing has occasionally been signalled during treatment with oxcarbazepine [20].

Psychiatric disturbances

The incidence of depression and psychosis in patients with epilepsy has been repeatedly found to be higher than the expected rate in the overall population. Depression occurs in about 30% of epileptic patients, anxiety disorders in 10–25% and psychosis in 2–7% [21]. Such disturbances often have a multifactorial origin. AEDs, as well as other treatments used in epilepsy, may exert variable psychotropic effects, which can be negative as well as positive (see Chapter 21).

Treatment with drugs with prominent γ-aminobutyric acid (GABA)-ergic properties (barbiturates, vigabatrin, tiagabine) and also topiramate, which has several mechanisms of actions, has been more frequently associated with depression. It has been shown that in patients with a long history of barbiturate therapy there is also a higher prevalence of major depressive disorder and of suicidal ideation [21].

In double-blind studies, an increased prevalence of depression has been observed in patients treated with vigabatrin (12.1% of patients treated with the active drug versus 3.5% of patients treated with placebo), tiagabine (3% versus 1%) and zonisamide (7.4% versus 3%). Topiramate and levetiracetam can also cause depression in some patients [21]. Recently, an analysis of all double-blind, placebo-controlled studies, performed with 11 AEDs for treatment of epilepsy as well as psychiatric disorders and other conditions, has revealed a significantly increased risk of suicidal behaviour and suicidal ideation in patients treated with the active drug in respect to patients treated with placebo. This observation has led to an Food and Drug Administration (FDA) warning [22].

Insomnia, nervousness and depression have been reported in clinical studies of patients treated with felbamate [9].

Detrimental effects on the behaviour of learning-disabled patients with epilepsy have been signalled during treatment with lamotrigine. This has been characterized as a 'release phenomenon', and considered a consequence of a positive effect of the drug on cognition without sedative properties [11]. In similar types of patients, levetiracetam has been associated with aggressive behaviour [23].

Psychosis is a generally rare but well-recognized complication of traditional AED therapy, and especially with ethosuximide. This complication often appears in the context of a significant improvement of seizure frequency and/or improvement of EEG abnormalities, and has been equated to forced normalization [24]. Psychoses have also been reported among patients treated with the newer AEDs such as felbamate, vigabatrin, levetiracetam, lamotrigine, tiagabine, topiramate, zonisamide and gabapentin [25].

Metabolic adverse effects

Megaloblastic anaemia, probably caused by folate and/or vitamin B12 deficiencies, has been described during treatment with phenobarbital, phenytoin or both. Vitamin K deficiency may lead to coagulation defects in neonates of mothers treated with enzyme inducers phenobarbital and phenytoin. Rickets and osteoporosis are the consequence of treatment with phenobarbital and phenytoin, and possibly also carbamazepine and valproate. Vitamin D deficiency, caused by drug-induced increased metabolism by enzyme-inducing AEDs, may partially explain these complications [26].

A dose-dependent thrombocytopenia can often be observed during treatment with valproate [8].

Several studies have demonstrated that enzyme-inducing AEDs are associated with elevations of lipoproteins and also homocysteine, which are risk factors for atherosclerosis [27].

Renal stones are a well-recognized concern with the use of topiramate and zonisamide. They are more common in men and are probably the consequence of the inhibition of the enzyme carbonic anhydrase, which results in increased urinary pH.

Inhibition of carbonic anhydrase may also lead to a reversible metabolic acidosis and, consequently, to a central hyperventilation syndrome, which is primarily observed in children treated with topiramate. Oligohidrosis and hyperthermia have been reported in patients treated with zonisamide and, less frequently, with topiramate [28].

Finally, several AEDs, with different and yet unknown mechanisms, can cause weight changes. Four AEDs – gabapentin, vigabatrin, pregabalin and valproate – and, possibly, carbamazepine cause weight gain. Obesity is an independent risk factor for diabetes and metabolic syndrome, coronary heart disease and hypertension.

Three drugs – felbamate, topiramate and zonisamide – commonly cause weight loss as a consequence of appetite suppression. In general, lamotrigine, levetiracetam and phenytoin do not have any effect on body weight [29].

Adverse effects on other organs or tissues

Several AEDs, particularly among the traditional medicaments, cause adverse effects in the endocrine system or other organs or tissues, often through the agency of endogenous metabolites. In some cases, these adverse effects may be considered as a consequence of known drug properties, and are dose dependent. For example, they can be the consequence of enzymatic induction in the case of phenobarbital, phenytoin or carbamazepine, or inhibition in the case of valproate, of cytochrome P450 (CYP) enzymes, which metabolize not only the AEDs but also other exogenous (vitamins) or endogenous (hormones, etc.) molecules. In many other cases, the mechanisms underlying these complications are not known.

Endocrine effects

Mild modifications of thyroid hormones of uncertain clinical significance can be observed during treatment with phenytoin, carbamazepine and valproate [27]. Carbamazepine, and more often oxcarbazepine, cause hyponatraemia and water retention. [30]. In some patients with prediabetes, insulin secretion may

Table 22.2 A selection of serious idiosyncratic reactions associated with individual antiepileptic drugs (AEDs).

	SJS/TEN	Liver toxicity	Pancreatitis	Aplastic anaemia	Agranulocytosis	Systemic lupus erythematosus
Carbamazepine	*	*	*	†	†	*
Ethosuximide	*	*	–	*	*	*
Felbamate	*	†	*	†	†	*
Gabapentin	*	*	–	–	–	–
Lamotrigine	†	*	*	*	–	–
Levetiracetam	–	*	*	–	–	–
Oxcarbazepine	*	*	–	–	–	–
Phenobarbital	*	*	–	–	*	*
Phenytoin	*	*	–	*	*	*
Pregabalin	–	–	–	–	–	–
Primidone	*	*	–	–	*	*
Tiagabine	*	–	–	–	–	–
Topiramate	*	*	*	–	–	–
Valproic acid	*	†	†	–	–	*
Vigabatrin	–	*	*	–	–	–
Zonisamide	*	*	–	*	*	–

From ref. 2.

For some of the reactions reported, information is insufficient to draw definitive conclusions about causality. (*) indicates that the specified reaction has been reported for that drug; (†) identifies reactions associated with a warning box in the US prescribing information monographs; and (–) indicates that the reaction has not been reported based on the sources of information stated above.

SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

be impaired by phenytoin and result in an abnormal glucose tolerance test.

Several studies show that carbamazepine, and to a lesser extent phenobarbital and phenytoin, can induce the metabolism of sex hormones, which might be a possible explanation for the hyposexuality experienced by some epileptic male patients. In women, treatment with valproate has been associated with polycystic ovary syndrome, which could be, partly at least, the consequence of drug-induced obesity and hyperinsulinaemia [8].

Connective tissue and cosmetic effects

Thickening of subcutaneous tissue, hirsutism, acne, hyperpigmentation, gingival hyperplasia and other unaesthetic features can be frequently observed in some epileptic patients who receive long-term phenytoin therapy. Other effects of AEDs on connective tissue include barbiturate-induced Dupuytren's contracture and shoulder–hand syndrome [27]. Thinning of hair, alopecia and curling of the regrown hair sometimes occurs with valproate treatment [8].

Other adverse effects

Carbamazepine has been occasionally implicated, particularly in older patients, in the production of a number of cardiovascular abnormalities, including conduction defects, congestive heart failure and hypertension.

Vigabatrin causes a specific bilateral concentric visual field constriction, which can be severe. This occurred in 31% of patients who had received vigabatrin for less than 4 years [31].

In rare cases, topiramate can induce ocular reactions, including acute secondary angle-closure glaucoma, acute bilateral myopia and suprachoroidal effusions [32].

Idiosyncratic cytotoxic or immunological adverse effects

Idiosyncratic adverse effects may involve various organs and tissues. A selection of the most important idiosyncratic reactions associated with AEDs is reported in Table 22.2.

Cutaneous reactions

Cutaneous manifestations are the most common of the idiosyncratic reactions caused by AEDs. They range from very benign mild skin rash to potentially life-threatening dermatological diseases.

Skin rashes, usually morbilliform or maculopapular in appearance, typically occur between day 5 and week 8 after the start of therapy. These are relatively common on therapy with phenobarbital, phenytoin and carbamazepine, with a frequency ranging from 5% to 15% [33]. Oxcarbazepine, the keto analogue of carbamazepine, is associated with a lower incidence of hypersensitivity reactions than carbamazepine. Lamotrigine can also cause this adverse effect. The incidence of rash is consistently higher when lamotrigine is added to valproate than when it is added to enzyme-inducing AEDs (19.5% versus 6.7%, respectively) [34]. Skin rashes may result from therapy with other AEDs, but their frequency is generally lower than that observed with the aromatic AEDs.

Drug-related rash with eosinophilia and systemic symptoms (DRESS), previously known as anticonvulsant hypersensitivity syndrome, is a severe acute drug reaction characterized by fever, skin eruption, eosinophilia, atypical lymphocytosis, arthralgia, lymphadenopathy and multiorgan involvement [35]. This complication is observed most frequently with phenytoin (2.3–4.5 cases per 10 000 exposures) and carbamazepine (1.0–4.1 cases per

10 000 exposures) [36]. Cases have also been reported with lamotrigine [34].

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; Lyell's syndrome) are bullous reactions accompanied by mucosal involvement and skin detachment. It has been suggested that the risk of SJS and TEN during the first 2 months of therapy is between 1 and 10 per 10 000 new users of carbamazepine, lamotrigine, phenytoin and phenobarbital, and consistently lower for valproate [2]. The recently described relationship of carbamazepine-induced SJS with a specific human leucocyte antigen (HLA) type in the Han Chinese is discussed below.

Haematological reactions

Aplastic anaemia occurs in the general population, with an incidence of 2–6 cases per million [37], and is the most serious drug-induced blood dyscrasia. The AED with the highest potential for causing this affection is felbamate, with a risk of 1 in 5000 or 1 in 10 000 [37]. Rare cases of aplastic anaemia have also been associated with carbamazepine, phenytoin, ethosuximide and valproate [2]. The incidence of carbamazepine-induced aplastic anaemia has been estimated at between 1 in 50 000 and 1 in 200 000 exposed patients [2].

Selective suppression of bone marrow cells may lead to agranulocytosis and pure cell aplasia, which are rarely observed during treatment with AEDs [2].

Pseudo-lymphoma syndrome is a rare condition, which may be part of DRESS syndrome spectrum, and has been associated mainly with phenytoin, although it can occur with other AEDs, particularly those with an aromatic structure [2].

Sporadic cases of thrombocytopenia, probably immune mediated, have been reported with carbamazepine, lamotrigine, phenytoin, felbamate, primidone and tiagabine [2]. Valproate-induced thrombocytopenia should not be considered as immune mediated.

Reactions affecting the liver and pancreas

Drug-induced liver toxicity may be caused by immune-mediated mechanisms or by direct cytotoxic damage. Aromatic AEDs have been recognized as a cause of severe immune-mediated hepatitis, which may be part of the spectrum of DRESS, or it may occur in isolation [38]. The exact incidence of liver toxicity associated with the aromatic AEDs is unknown, although for carbamazepine the risk has been estimated at 16 cases per 100 000 treatment years [2]. Rare cases have also been described of severe lamotrigine-induced liver toxicity [2], sometimes in association with multisystem organ failure and disseminated intravascular coagulation.

Valproate and felbamate are associated with the greatest risk of potential liver toxicity. The pathogenic mechanism of valproate-induced hepatotoxicity is probably characterized by a direct toxic action of valproate and/or its metabolites [39], and differs substantially from those associated with liver toxicity caused by aromatic AEDs. The incidence of fatal valproate-induced hepatotoxicity varies in relation to age and associated therapy. The highest risk (1:500) is in children younger than 2 years on polytherapy. In older patients, the risk has been estimated at 1:12 000 with polytherapy and 1:37 000 with monotherapy [39]. However, in recent years, the overall incidence of valproate-induced fatal liver toxicity seems to have decreased.

The mechanism of this drug-induced liver toxicity due to felbamate is not clearly understood, but may depend on the formation of reactive toxic metabolites [40]. There is evidence that aldehydes generated from felbamate can induce liver damage via a direct cytotoxic mechanism [40]. Immune-mediated mechanisms, however, may also be involved. The risk of fatal hepatic failure due to felbamate is estimated at approximately 1 per 26 000 to 34 000 exposures [2].

Pancreatitis is a rare complication of valproate therapy. This condition can develop at any time, but most commonly occurs during the first year of treatment or after an increase in dosage. Age below 20 years, polytherapy, chronic encephalopathy and haemodialysis are possible risk factors. Estimated incidence is 1:40 000 [2,8].

Systemic lupus erythematosus

Carbamazepine and, to a lesser extent, phenytoin, ethosuximide, valproate, lamotrigine and other AEDs can rarely induce or activate systemic lupus erythematosus. This drug-induced condition is sometimes not easily differentiated from the idiopathic form of the disorder [2].

Prevention and management of adverse effects

Several measures are important. Before prescribing a drug, the adverse effects profile should be tailored to the individual patient. Once on a medication, steps can be taken that prevent or minimize these complications. At the beginning of therapy and during dose escalations, clinical monitoring for early identification of possible adverse effects should be regularly performed.

Analysis of risk factors

Age

Age is a critical influence on a number of adverse effects. Children are especially predisposed to long-lasting consequences of cognitive and behavioural effects of AEDs [10]. Cognitive alterations, hyperactivity and other conduct disorders are frequently observed in children treated with phenobarbital, although these symptoms may also occur in association with phenytoin, benzodiazepines, gabapentin and vigabatrin [11]. Fragile elderly patients, often with several co-morbidities and treated with many drugs, are also at special risk for development of cognitive and motor adverse effects induced by several AEDs [41].

Differences in drug metabolism may explain why some AED-induced idiosyncratic adverse effects develop more frequently in children [2]. Glucuronide conjugation is reduced while cytochrome-mediated reactions are faster in infants and children than in adults, and this can result in an increased production of reactive metabolites [41]. Lamotrigine-induced serious and non-serious skin rashes [42] occur more frequently in children than in adults. The incidence of SJS in children started on lamotrigine has been estimated to be as high as 1:100, compared with 1:1000 in adults [43].

Young age is also a major risk factor for valproate-induced hepatic injury, for which the highest risk is recorded in infants

below the age of 2 years [39]. This might be due to the higher prevalence of predisposing conditions such as inborn errors of metabolism in infants, as well as pharmacokinetic factors such as accumulation of the toxic metabolite 4-en-valproate, the concentration of which is negatively correlated with age [2].

Idiosyncratic reactions occur at a relatively high frequency also in old age. In a controlled trial in elderly patients with new-onset epilepsy, as many as 19% of those exposed to carbamazepine withdrew in the first 2 weeks because of skin rashes, despite use of a low dose (100 mg/day) [44].

Medical and psychiatric co-morbidities

Concomitant diseases may strongly influence tolerability to several AEDs.

The probability of developing a CNS dose-dependent adverse effect can be influenced by the presence of a structural brain lesion. Brain damage also predisposes to 'off-target pharmacology'. For example, basal ganglia damage and mental retardation are frequently reported in patients with phenytoin-induced choreoathetosis [16].

Psychiatric adverse effects of AEDs are more frequently observed in predisposed patients. It has been suggested that vigabatrin, topiramate and ethosuximide should be avoided in patients with a previous history of psychotic episodes and levetiracetam used only with great caution in this population of subjects [23].

The risk of cytotoxic or allergic idiosyncratic adverse effects is also strongly increased in the presence of several diseases. Rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, panhypogammaglobulinaemia, idiopathic thrombocytopenic purpura, high serum antinuclear antibody titres, and a history of cytopenia or hypersensitivity to other AEDs are considered as risk factors for felbamate-induced aplastic anaemia [2]. Systemic lupus erythematosus, other immune system disorders, corticosteroid therapy and a family history of serious rashes are also risk factors for hypersensitivity reactions to other AEDs [2]. Infectious diseases are also associated with a higher frequency of allergic drug reactions [2]. HIV infection also seems to be a risk factor for hypersensitivity reactions to AEDs. In general, the presence of such risk factors justifies the preferential use of AEDs with a low allergenic potential such as gabapentin, levetiracetam, pregabalin, clobazam, tiagabine, valproate and, possibly, topiramate.

Valproate-induced liver toxicity is another example of an idiosyncratic adverse effect, the frequency of which is greatly increased in patients with specific concomitant affections. Several metabolic disorders, including urea cycle defects, organic acidurias, multiple carboxylase deficiency, mitochondrial or respiratory chain dysfunction, cytochrome aa3 deficiency in muscle, pyruvate carboxylase deficiency and pyruvate dehydrogenase complex deficiency, all predispose to valproate toxicity [2]. Patients with GM1 gangliosidoses type 2, spinocerebellar degeneration, Friedreich ataxia, Lafora body disease, Alpers–Huttenlocher disease and myoclonic epilepsy with ragged red fibre (MERRF) disease are also more susceptible to valproate hepatotoxicity [2].

Associated drugs

It is well known that the frequency of CNS dose-dependent adverse effects is increased by polytherapy. Total drug load, pharmacodynamic and pharmacokinetic interactions are possible explanations. Every effort should be made to reduce the number of concomitant treatments. Patients whose seizures have not responded to an initially prescribed AED are less likely to develop adverse effects by being switched gradually to an alternative drug also given as monotherapy [45].

Co-medication can also influence susceptibility to idiosyncratic reactions. Concomitant treatment with valproate, in particular, increases the risk of lamotrigine-induced hypersensitivity [34]. Enzyme-inducing AEDs increase the incidence of valproate-induced liver toxicity, pancreatitis, hyperammonaemia and encephalopathy [39]. Ketogenic diet is often associated with reduced carnitine stores and may therefore increase the risk of valproate-induced hyperammonaemic encephalopathy and hepatotoxicity [46].

The risk of oxcarbazepine and carbamazepine-induced hyponatraemia and water retention is increased in elderly patients who are also treated with some diuretics or selective serotonin reuptake inhibitor (SSRI) antidepressants.

Genetic factors

More than 40 years ago, patients were identified who were slow metabolizers of phenytoin and therefore particularly susceptible to dose-dependent adverse effects of this drug [12]. Today, it is known that mutations of the gene coding for *CYP2C9*, one of the two P450 isoenzymes which metabolize phenytoin, appear to be responsible for this effect [47].

The occurrence of similar idiosyncratic reactions to AEDs in identical twins and in families suggests a genetically determined predisposition [2], possibly with an autosomal pattern of inheritance. Siblings of patients who had immune-mediated idiosyncratic reactions to aromatic AEDs such as phenytoin, carbamazepine, phenobarbital and primidone have up to a 25% probability of experiencing a similar reaction when exposed to a drug of the same class (cross-reactivity).

The higher incidence of carbamazepine-induced SJS in Chinese compared with white patients also reveals that genetic factors must be involved. It has been recently observed in the Han Chinese population that carbamazepine-induced SJS and TEN, but not carbamazepine-induced maculopapular reactions or DRESS, are strongly associated with the HLA-B*1502 allele [48]. Interestingly, the role of ethnicity in these reactions is emphasized by recent data confirming that an association between carbamazepine-induced SJS and the HLA-B*1502 allele is present in Asians, but not in whites [49]. A genetic test has recently been made available on the market for detection of the HLA-B*1502 allele and the FDA now recommends execution of this test for those patients with ancestry across Asia and South Asia before starting carbamazepine treatment [50].

Strategies for prevention or minimization of adverse effects

Low doses at the beginning of a treatment, slow titration, the search for minimal effective maintenance doses and appropriate posological schemas can greatly reduce the risk of adverse effects [45].

Starting dose and titration rate

The frequency and severity of most adverse effects is influenced by the starting dose and by the speed of dose incrementation. For this reason, care should be taken not to exceed the recommended initial dose and speed of titration of every drug, and indeed in routine practice to start with lower doses and to increase doses more slowly.

Tolerance to CNS adverse effects is common. Gradual titration can prevent such effects by allowing the development of pharmacodynamic tolerance. A slow titration may also minimize CNS adverse effects in practice by permitting early detection of subtle or prodromal signs which thus warn against further dose increase.

There is a common misconception that the idiosyncratic adverse effects are unaffected by dose or titration rate. In fact, some immune-mediated reactions occur only when a critical dose threshold is reached. Several lines of evidence indicate that the risk of allergic reactions decreases when treatment is started at a low dose and is increased gradually, possibly because slow titration may allow desensitization to occur [43]. A relation between starting dose (and titration rate) and the incidence of cutaneous reactions has been particularly demonstrated in therapy with lamotrigine [34], carbamazepine and phenytoin [33]. For example, in lamotrigine monotherapy trials in adults, rash occurred in 6.1% of patients when the dose in the first treatment week was <31 mg/day, and in 20.5% of patients when the dose was between 62.5 and 125 mg/day [34].

Individualization of minimal effective dose of a drug

The prescription of excessively high dosages of AEDs is relatively common [44]. AEDs have a narrow therapeutic ratio, and with these drugs, particularly for toxic effects, dose–response relationships vary greatly from one patient to another. Every effort should be made to identify, wherever possible, the lowest effective dose.

Daily regimens and chrono formulations

Fluctuations of blood levels can be responsible for some intermittent dose-related CNS adverse effects. It has been observed, in patients treated with carbamazepine who complain of intermittent diplopia and ataxia, that these adverse effects can be closely correlated with total and free carbamazepine blood levels [12]. The same applies to tiagabine, an AED with a short half-life, the metabolism of which can be induced and the absorption of which is greatly affected by the relationship of dosing to meals. In such cases, an increase in the number of daily administrations or, in the case of carbamazepine, a controlled-release formulation often improves drug tolerability [51].

Monitoring drug therapy

Proper consumption of therapy should be constantly discussed with the patient. Some patients may occasionally decide to increase the dose of a drug when they experience a seizure. Other patients may take their therapy inconsistently because they may forget one daily dose (it is known that compliance worsens with increasing number of daily doses). In all these cases, higher fluctuations of blood levels of an AED may increase not only probability of seizure recurrence, but also the appearance of some dose-dependent adverse effects.

Monitoring serum drug concentrations

The measurement of blood levels in patients with apparently dose-dependent adverse effects, especially of drugs with a narrow therapeutic index and/or non-linear kinetics such as phenytoin or carbamazepine, is of crucial importance.

However, even though knowledge of AED plasma levels can be useful for seeking the optimal dose of a drug, data can be misleading if misinterpreted. It should be realized that reference therapeutic ranges are only probabilities and that patients with clinical response at serum AED concentrations below the lower limit of these ranges should not have their treatment increased. A measure which can be useful is the identification of the concentration of an AED at which an optimal response is achieved [45]. In other clinical circumstances, for instance when changing doses of concomitant medication or formulations, serum drug monitoring can be useful in preventing seizure recurrence or adverse effects.

Other measures

Other measures for preventing adverse effects include increased water intake in male patients treated with topiramate or zonisamide to avoid kidney stones, or decreased water intake in patients treated with oxcarbazepine who are at risk of hyponatraemia, for instance the elderly or patients taking other drugs which may cause hyponatraemia [28].

Early identification

The key for the early identification of adverse effects is clinical monitoring. Vigilance is important, as is the awareness of patients, doctors and relatives of potential complications and the symptoms that may herald the occurrence of an adverse effect.

Identification of subtle toxicity

Although dose-dependent adverse effects are frequent and have a major impact on a patient's quality of life [52], they are not always easily identified. Subtle motor or cognitive effects can be neglected in the outpatient setting. Some relevant adverse effects (e.g. reduced libido or impaired sexual potency) are less likely to be reported spontaneously, and need to be investigated specifically. In one clinical study, nearly one-third of epileptic patients on treatment with AEDs who were screened with a self-report instrument [the adverse events profile (AEP)] met criteria for drug toxicity. When clinicians, for the evaluation of their patients, could utilize information from this instrument, drug treatment adjustments led to an improvement of drug toxicity score. Interestingly, the quality of life score [52] was significantly inversely correlated with AEP score but was not correlated with seizure frequency (Fig. 22.1). This problem is compounded by the fact that, after a number of months of drug treatment with an AED, some patients forget what normal cognitive and motor functions were like [5].

Neurophysiological examinations (quantitative EEG measurements, posturography, quantitative analysis of ocular movements, etc.) aimed at measuring subtle toxic effects of AEDs on CNS, though of a certain utility as a research tool, have no practical use for clinical monitoring [12]. One exception is the case of visual field examinations, which should be performed before the start of treatment and at regular intervals during treatment with

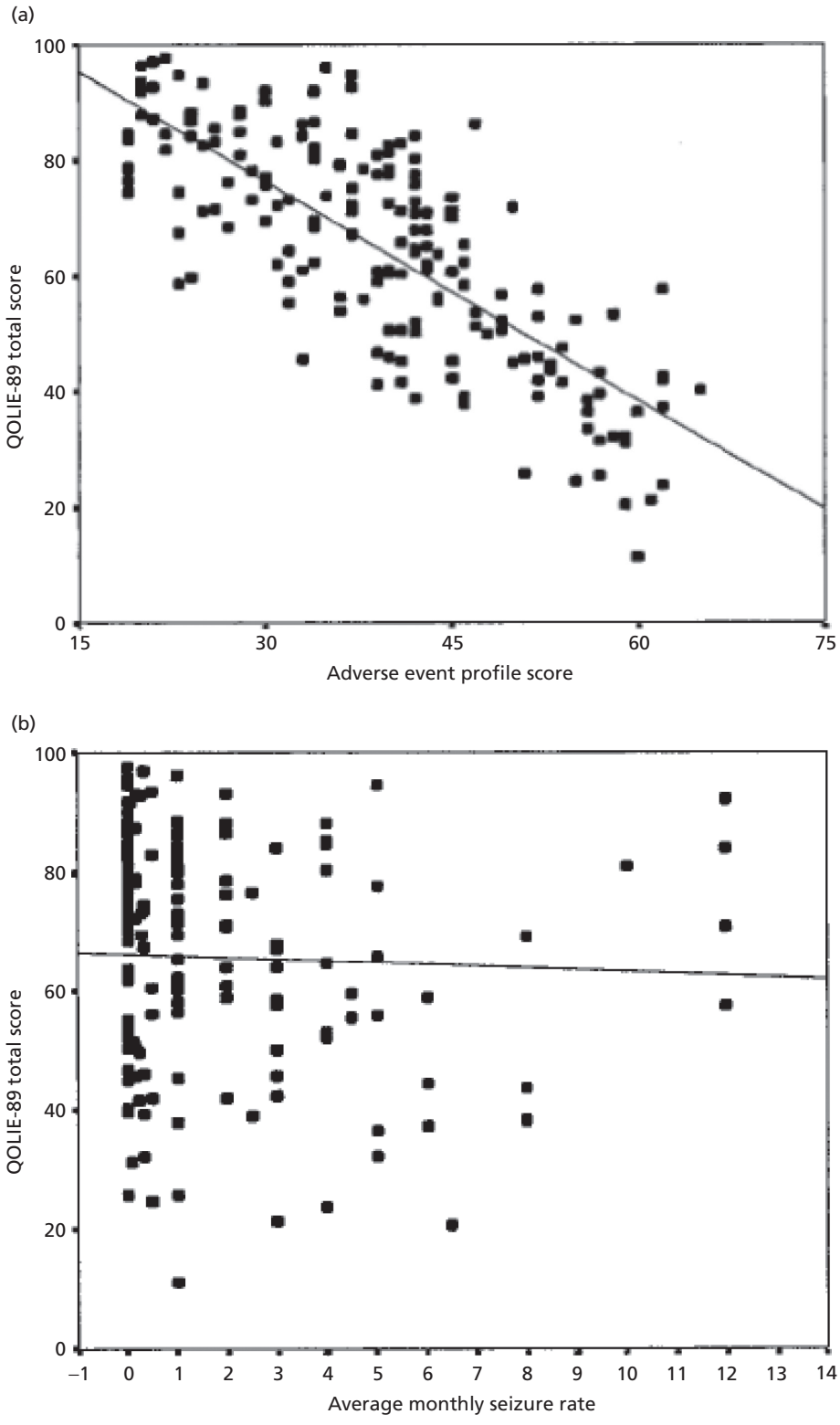

Fig. 22.1 Comparison of baseline Quality of Life in Epilepsy (QOLIE)-89 total score with (a) baseline adverse events profile (AEP) score ($r = –0.76$; $P < 0.001$) and (b) average monthly seizure rates (partial correlation controlling for AEP score; $r = 0.001$; $P = 0.99$; $n = 200$). From ref. 52.

vigabatrin for monitoring of retinal toxicity induced by this drug [31].

Early identification of idiosyncratic reactions

Early identification of idiosyncratic drug reactions may be life saving. It is most important to inform patients and relatives about potential adverse effects and to report warning symptoms or signs.

One issue concerns the utility of laboratory monitoring in the early identification of subclinical allergic or cytotoxic idiosyncratic reaction in asymptomatic patients. Package inserts of several AEDs include recommendations about laboratory

Table 22.3 Baseline screening laboratory examinations.

Complete blood count with differential and platelets
Glucose
Blood urea nitrogen
Electrolytes
Calcium
Phosphorus
Magnesium
Creatinine
Urate
Serum iron
Cholesterol
Bilirubin
Alkaline phosphatase
Aspartate aminotransferase
Alanine aminotransferase
Total protein
Albumin
Globulin
Prothrombin time
Thromboplastin time
Complete urine analysis

Table 22.4 Management of AED-induced immune-mediated idiosyncratic reactions. Prompt recognition of the reaction and withdrawal of the offending drug are essential management steps.

Most patients need a complete blood count and biochemistry (including thyroid function tests) for the evaluation of internal organ involvement. Such tests should be repeated at 3 months. Additional investigations (e.g. chest radiography, bone marrow or skin biopsy) may be indicated depending on clinical presentation
Patients with drug rash with eosinophilia and systemic symptoms (DRESS) require hospitalization for symptomatic and supportive therapy. Patients with Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) should be preferentially managed in burn units
Treatment with corticosteroids is advisable, controversial or contraindicated, depending on the condition. Other treatments (e.g. immunoglobulins, immunosuppressants, organ transplantation, etc.) should be considered depending on clinical presentation
An appropriate AED should replace the withdrawn AED, to prevent recurrence of seizures and status epilepticus. AEDs expected to be involved in cross-reactivity reactions or to aggravate the underlying pathology should be avoided
Patients with serious hypersensitivity reactions should not be re-challenged. The value of patch tests and *in vitro* tests for assessing causality and predicting risk of recurrence is limited

From ref. 2.

monitoring. However, there is no evidence of any real usefulness of such examinations for prevention of these serious complications [2,5] and several authors [5] have concluded that routine screening is neither cost-effective nor of significant value.

A reasonable approach is to carry out laboratory monitoring (Table 22.3) in the following situations: (1) before starting treatment (or adding a new AED), to establish a baseline against which to interpret any subsequent change in clinical status; (2) in high-risk groups; and (3) in patients with impaired ability to communicate [5]. However, for high-risk drugs, most notably felbamate or valproate (in young children), it would be wise to follow package instructions.

Traditional AEDs can cause a reduction of blood levels of some vitamins. In selected cases it is useful to measure levels of vitamin D, folic acid and vitamin B_{12}.

Treatment

Dose reduction and/or modification of dosing schemas (more frequent daily administrations, higher dose in the evening in the case of sedating drugs), chrono formulations and/or a lower titration speed will be sufficient to avoid or manage several of the most common dose-related adverse effects. In a few cases, specific treatments can be given to alleviate the intensity of some adverse effects, for example the use of propanolol, amantadine and acetazolamide to alleviate valproate-induced tremor.

However, some patients do not tolerate certain treatment-emergent adverse effects even at low doses of an AED, and in this case it is necessary to discontinue the drug. In these situations, it is wise to try a new AED with a different profile of tolerability (e.g. a patient who complains of somnolence during a treatment with levetiracetam might be switched to lamotrigine, which is less sedative). Similar recommendations could be given in the case of rare but not serious adverse effects that are caused by an unusual interaction of the drug with the host organism (e.g. the development of dyskinesia or tics).

The case is different for serious reactions (or reactions potentially evolving into severe conditions) which require immediate discontinuation of the offending agent. In the majority of cases, it is appropriate to substitute another AED considered to be reasonably safe in the specific context. In patients with hypersensitivity reactions to an aromatic AED, other aromatic anticonvulsants should be avoided, and agents with a low allergenic potential, such as benzodiazepines, levetiracetam, gabapentin and pregabalin, are probably safe. Topiramate and valproic acid may also be safe, but they are less suitable for fast titration. Also, valproic acid, being an inhibitor of epoxide hydrolase, may delay the detoxification of residual reactive metabolites.

In patients with early symptoms or also the suspicion of an idiosyncratic reaction, baseline (see Table 22.3) and specialized hematochemical tests should be immediately performed. In patients who develop a hypersensitivity syndrome (hepatitis, pancreatitis, DRESS, etc.) the full gamut of laboratory tests should be carried out to evaluate a possible multi-organ involvement according to the nature of the suspected incipient reaction.

For the management of immune-mediated hypersensitivity reactions, symptomatic and supportive therapy may be indicated based on the clinical presentation. Treatment with corticosteroids is controversial, though most physicians elect to start prednisone at a dose of 1–2 mg/kg if symptoms are severe [2]. Patients with specific organ involvement need to be managed by the appropriate specialist. Patients with SJS and TEN in particular should be managed, preferably in a burns centre, to ensure adequate supportive management in terms of wound care, hydration, nutritional support, and prevention of infection and other complications (Table 22.4).

In selected cases, to avoid the situation whereby a patient is erroneously labelled as 'hypersensitive' to an AED, it is important to make confirmatory tests.

Re-challenge, for diagnostic purposes, remains the only conclusive method to confirm causality, and may be appropriate for certain reactions (e.g. many idiosyncratic effects affecting the CNS) which do not involve immune-mediated hypersensitivity or cytotoxicity. However, re-challenge is not justified in those who have experienced serious reactions [2].

Presently, there are some tests available for diagnosis of immune-mediated hypersensitivity reactions, namely patch and prick tests, and *in vitro* tests such as the lymphocyte transformation test and the lymphocyte assay. While the skin patch test has been proven to be very useful for prediction and diagnosis of some types of hypersensitivity reactions such as allergy to beta-lactam antibiotics, the diagnostic value of this test is yet to be determined for diagnosis of allergic reactions to AEDs. *In vitro* tests are primarily research tools, and their negative and positive predictive values are still unknown [2]. Because of the above considerations, all these tests are rarely conducted. If these tests are performed, results should be interpreted cautiously. In fact, a negative test result does not exclude the possibility of a drug reaction, and in these cases re-challenge should be done only when absolutely necessary and under close medical control [2].

Traditional AEDs have several metabolic effects which, in some cases, mainly during long-term treatment, may lead to some diseases. The most important example is probably the effect on bone mineral density by phenobarbital and phenytoin and, perhaps, by carbamazepine and valproic acid. Rickets and osteoporosis are possible consequences of this metabolic effect. While treatment of choice for rickets is vitamin D, bisphosphonates are used for the treatment of osteoporosis in both children and adults [25]. Megaloblastic anaemia, which can be observed during therapy with phenobarbital and phenytoin, usually responds to folate therapy.

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23 Ketogenic Diets

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Introduction

The history of the ketogenic diet has been described in great detail in recent reviews [1]. The use of diet manipulation to control seizures has its origins back to biblical times, with descriptions of Jesus curing 'possessed' patients with prayer and fasting. In 1911, Guelpa and Marie [2] reported the use of fasting to improve epilepsy in the French population. Interest in the USA originates with Geyelin [3], who reported at the 1921 American Medical Association convention the successful use of 3 weeks of fasting for 26 patients with severe epilepsy. Much of his protocol was based on the work of Conklin [4], an osteopathic physician from Michigan who treated a 10-year-old boy with the help of a faith healer, Bernarr Macfadden, and a 'water diet'.

Research into the ketogenic diet soon followed as the word of this successful advance in epilepsy spread. Gamble and Howland subsequently investigated the ketogenic diet at the Johns Hopkins Hospital [5]. Early research indicated a potential role of acidosis, dehydration and ketosis [6–8]. Wilder [8], from the Mayo Clinic, first proposed attempting an actual diet in order to maintain children and adults on this therapy for extended periods of time. This ketogenic diet mimicked starvation by providing a regimen of 1 g/kg protein, 10–15 g of carbohydrate and the remaining calories per day as fat [9]. A ratio of fats to carbohydrates and protein of typically either 3:1 or 4:1 was used to maintain ketosis. Calories were based on the basal metabolic rate plus 50%. This is quite similar to the ketogenic diet still in use today, with slightly less insistence on calorie and fluid restriction.

Further reports of efficacy followed [10], especially in children, but were later ignored by the discovery of phenytoin in 1938. As the era of anticonvulsants began, the ketogenic diet was viewed as rigid, expensive and restrictive. A medium-chain triglyceride (MCT) oil-containing diet was developed to make the diet easier to use [11]. A study comparing the classical ketogenic diet, the MCT oil diet and a modified MCT oil diet revealed similar efficacies, with 81% of patients on both diets having a greater than 50% reduction in seizures [12]. This diet allows for more carbohydrates than the classic long-chain triglyceride (LCT) ketogenic diet, and is still widely used in the UK. New research regarding this diet will be discussed later in this chapter. As new anticonvulsants continued to become widely available, many more epileptologists felt the diet was not useful. Although several centres, mostly in the USA, continued to use the diet actively [13], the number of patients treated with the diet became very small.

In 1992, things changed dramatically. A 2-year-old boy named Charlie was admitted to the Johns Hopkins Hospital because of intractable epilepsy [14]. Charlie was started on the ketogenic diet and within weeks had respnded extremely well. As a result, Charlie's father created the Charlie Foundation, which informs patients and physicians about the ketogenic diet and remains very active (www.charliefoundation.org). Since then, many medical centres have started using the ketogenic diet, and several large studies have demonstrated its effectiveness [15–17]. The ketogenic diet is now well established in the medical community for the treatment of childhood (including infantile) epilepsy, and it is reimbursed by insurance companies including Blue Cross and Blue Shield in the USA [18]. Other parent advocacy groups, such as Matthew's Friends in the UK (site.matthewsfriends.org), and collaborative research from individual nations' child epileptologists, have led to the ketogenic diet being available nearly everywhere in the world with the exception of large parts of Central America and Africa [19]. The ketogenic diet (as the modified Atkins diet) has had a recent resurgence for the treatment of adults with epilepsy, now 80 years after it was initially reported in this age group.

The ketogenic diet requires skill and commitment to initiate and to maintain, especially in older children and adolescents. A well-trained team of neurologists and dietitians is needed to initiate and also monitor the ongoing use of the diet. The effects on seizures, in children whose seizures were previously intractable, can be dramatic. The diet requires commitment by the families, and ongoing medical advice and support by the treating team. An international, multicentre consensus statement on the ideal clinical management of the ketogenic diet is now in press [20].

Mechanisms of action

The ketogenic diet mimics the starvation state by utilizing a high-fat, adequate-protein (1 g/kg body weight), low-carbohydrate diet. This diet causes a dramatic shift in metabolism that affects the entire body. The actual mechanism by which the ketogenic diet helps suppress epilepsy remains unclear despite decades of research [21]. Initial research theorized that acidosis, dehydration and hyperlipidaemia reduced seizures, but these hypotheses shifted towards ketosis 20 years ago [1].

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Ketone bodies (acetoacetate, acetone and β-hydroxybutyrate) are formed in the liver, often preferentially when the body is forced to use stored fats for energy [1]. Long-chain fatty acids are released from adipose tissue in a starvation state, transported via plasma to the liver cytosolic membrane, and then enter mitochondria via the carnitine acyltransferase system [22]. Once inside the mitochondria, fatty acid oxidation converts the fatty acids to acetyl coenzyme A (CoA). Acetyl CoA is then converted to ketone bodies. Medium-chain fatty acids are also converted to acetyl CoA via acyl-CoA synthetase, but are able to bypass the carnitine acyltransferase system.

Ketone bodies are utilized efficiently by the body, and can provide 65% of the brain's energy requirements in starvation states [23]. Ketone bodies are transported into the brain after being synthesized in the liver via a monocarboxylic acid transporter [24]. Once there, they are both metabolized via the tricarboxylic acid cycle into energy and converted into cholesterol, lipids and fatty acids [1]. Elevated levels of ketone bodies also inhibit glucose metabolism in the brain, returning the glucose to the liver for gluconeogenesis as lactate and pyruvate [25].

The exact mechanism by which (or if) elevated ketone bodies in the brain reduce seizures is less clear. Uhlemann and Neims [26] developed the first animal model of the ketogenic diet in 1972. Mice were made ketotic using a diet and were then tested for protection against electroshock- and bicuculline-induced seizures. Ketonaemia protected the mice against both methods of seizure induction, with loss of this protection within 3.5 h of diet discontinuation [26]. In addition, younger mice (16 days old) were able to produce higher ketonaemia and thus longer seizure protection than older mice (40 days old). Other studies of rats have reproduced this protective effect [26,27].

More recent research has attempted to elucidate the mechanisms by which ketone bodies affect seizure thresholds. There has been some suggestion that ketone bodies are structurally similar to γ-aminobutyric acid (GABA) and may act as anticonvulsants in themselves [19,28]. Thio *et al*. [29], however, recently demonstrated that direct application of ketone bodies to rat hippocampus failed to directly affect synaptic transmission.

However, in recent years, the importance of ketosis in the mechanism of action of the ketogenic diet has been questioned

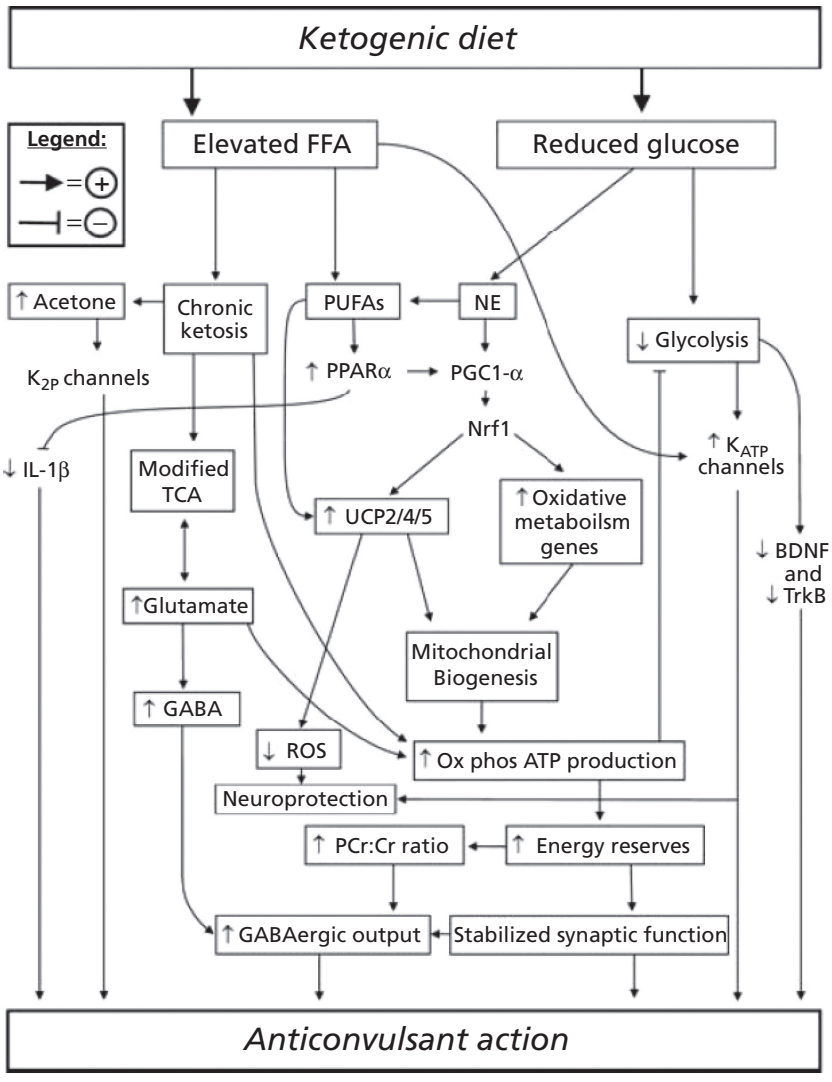

Fig. 23.1 Potential mechanisms of action of the ketogenic diet. Reproduced with permission by *Epilepsia* and Dr Jong Rho [30].

[30]. It may be more accurate to say that ketosis is necessary as a sign of a shift in body metabolism, but may not be sufficient to lead to seizure reduction. Studies of alternative diets such as the low glycaemic index treatment suggest that the efficacy of the diets is related to either glycolysis inhibition or stabilization of serum glucose levels. Genetic studies have also implicated the diet's effects on the mitochondrial processes of oxidative phosphorylation, and suggested that energy production in these cell organelles is the final end-pathway of diet action [31]. Another recent study demonstrated that the ketogenic diet may act via activation of potassium adenosine triphosphate (ATP) channels and a negative feedback effect on glycolysis [32]. Whether these diets work through increased fats, decreased glucose, caloric restriction or several other pathways to achieve this goal is unclear. A summary of potential mechanisms under active investigation is in Figure 23.1.

Seizure outcomes

Many retrospective studies of the ketogenic diet's efficacy have been performed. Initial findings by Peterman in 1925 [33] showed that 95% of children on the ketogenic diet experienced a reduction in seizures of more than 50%. Reports of results from the 1980s also showed efficacy, with 67% of children showing greater than 50% improvement in their seizures [34]. However, these studies were typically retrospective and single centre.

Two prospective uncontrolled studies in 1998 [15,16] brought the ketogenic diet's usefulness for intractable epilepsy to the medical mainstream. A multicentre study from seven sites in the USA enrolled 51 children aged 1–8 years on a 4:1 ketogenic diet [15]. At 3 months, 54% had a greater than 50% reduction in seizures, compared with 55% at 6 months and 40% at 1 year [15]. In addition, side-effects were uncommon, and 47% stayed on the diet to at least 1 year.

Johns Hopkins published its single-centre, prospective experience with 150 children that same year [16]. These children were of similar ages and had intractable epilepsy (mean 410 seizures per month, 6.2 prior anticonvulsants). Efficacy was similar to the multicentre study, with 50% having greater than 50% seizure reduction at 1 year and 27% having greater than 90% seizure reduction. This original 150-patient cohort was subsequently followed for 3–6 years [35]. Of these children, 44% were still more than 50% improved, and 78% of those who remained on the diet for at least 12 months were more than 50% improved.

At the time of writing, nearly 100 prospective and retrospective studies of the ketogenic diet have been completed, many multicentre in design. Results are surprisingly similar between studies, as outlined in a recent meta-analysis [34]. In general, approximately 55–60% of children started on the ketogenic diet will have at least a 50% seizure reduction after 3–6 months of therapy. Between 25% and 30% will show even more improvement, with at least 90% seizure reduction. Approximately 10–15% of all children started on the ketogenic diet will become seizure free, often permanently. This improvement occurs rapidly, often within 2–4 weeks of diet onset [36]. The diet also appears to work more quickly, after a median of 9 days, in those children who are fasted for 24–48 h before the diet is initiated. Considering that these results are noted in a very intractable population, one would hypothesize that the ketogenic diet is a better option for difficult-to-control seizures than medications.

A randomized, controlled study of both the classic (LCT) and MCT diets has been recently completed at Great Ormond Street Hospital in London in a manner to prove this hypothesis [37]. In this study, 145 children were all started on one of the two diets after either a 4-week (active) or 12-week (control) period of continued and unchanged medication therapy, with each child therefore serving as his/her own control. The ketogenic diet was dramatically more likely to result in seizure improvement – the results showed that children receiving the ketogenic the diet experienced 38% fewer seizures than previously, compared with an *increase* in seizures of 37% in the control group ($P < 0.001$) [37]. Five children in the diet group had a > 90% seizure reduction, whereas none in the control group did. There was no difference between the classic and MCT diet in regards to efficacy.

A study has been completed recently in order to address prospectively the efficacy of the ketogenic diet in a double-blind, randomized, placebo-controlled manner at Johns Hopkins Hospital [38]. Children were started on a ketogenic diet but were then given a solution of either placebo (saccharin) or 60 g glucose to take orally daily. After 5 days, each subject was crossed over to restart the ketogenic diet with the alternative solution. EEGs, clinical seizure activity and ketones were monitored to assess efficacy. The study showed a significant reduction in seizures over the total 12-day period, with a median decrease of 34 seizures per day ($P = 0.003$). However, there was no difference between the saccharin and glucose arms in regards to EEG change, and only a trend towards reduced parent-observed seizures ($P = 0.07$). This research did demonstrate, despite the non-significant results, that a double-blinded study of the ketogenic diet can be completed successfully using this unique design.

A possible additional benefit of the ketogenic diet is a reduction in medication costs. In one study [39], 74% of patients had their medications reduced with a cost reduction of 70%. The average estimated cost reduction per child per year was US$530 in this report. It is also important to realize that many parents start the ketogenic diet not only for seizure control but for cognitive improvement as well as medication reduction [40]. Understanding and addressing these parental concerns may lead to better ketogenic diet compliance.

Ketogenic diets and adults

In 1930, the ketogenic diet was perceived as a viable approach to intractable adult epilepsy in a study of 100 adults by Dr Barborka [41]. In this study, patients aged 16–51 years were started on the traditional ketogenic diet and 56% responded. This is surprisingly similar to most studies today in children, yet the diet was seen as less beneficial for adults. In fact, in the discussion, Dr Barborka stated, 'there seems to be no question but that the patient who can be afforded the best opportunity for treatment is the child or young adult . . . whereas older patients . . . are the least likely to be benefited' [41].

The ketogenic diet fell out of favour and was not specifically reported on in adults again until Dr Joseph Sirven and his group from Jefferson Medical Center in Philadelphia first presented their research in abstract form 69 years later [42]. In this study, 11 adults (9 women) were treated with a traditional, 4:1 ratio, ketogenic diet with 55% having a > 50% improvement after 8 months of therapy [42]. Cholesterol increased from a baseline of 208 to 291 mg/dL over the study period.

In 2008, the results of a prospective, open-label trial of the modified Atkins diet in adults was reported [43]. Further details about this 'alternative' ketogenic diet, which induces ketosis with less dietary restrictions, are discussed in the following section. Results were encouraging, with 47% having a > 50% improvement after 3 months using an intent-to-treat analysis [43]. Cholesterol increased slightly, but the median weight loss of 6.8 kg was motivational for most adults who were overweight to start. Further adult studies of the modified Atkins diet are under way.

Alternative ketogenic diets

In 2002, the experience of treating two children at Johns Hopkins led to the creation of an alternative version of the ketogenic diet that has now been studied in a total of 90 children and adults from three countries [43–45]. This diet has been called the 'modified Atkins diet'. The first child was a 7-year-old girl with intractable complex partial seizures who was 1 month away from her scheduled admission for the ketogenic diet. Her parents were counselled to restrict carbohydrates to prepare her for the restrictions of the ketogenic diet. Within 2 days of following the induction phase of the Atkins diet (<20 g/day of carbohydrates), her seizures had stopped, and 1 week later her ketogenic diet admission was cancelled. She remained on the Atkins diet for over 3 years. A second child, age 10 years, had stopped the traditional ketogenic diet 1 year prior due to absence seizure freedom. When his seizures began to recur, his mother started refeeding him the high-fat and low-carbohydrate foods *ad lib* that he had eaten in the past. Ketosis recurred and seizures stopped once again.

These two children led to prospective studies in using the 'modified' Atkins diet, which initially restricts carbohydrates to 10 g/day (15 g/day in adults), encourages high-fat foods, but does not require an admission or fast [44]. Protein, fluids and calories are not limited (in fact, they are encouraged). In both children and adults, results are surprisingly similar, with 47% of patients with intractable epilepsy having at least a 50% reduction in their seizure frequency [43,44]. Ketosis occurs, but generally decreases over several months on this diet, yet does not appear to correlate with efficacy except during the first month only [45]. Side-effects include increased cholesterol and blood urea nitrogen (not creatinine, however) and weight loss [44,45]. Interestingly, in adults, weight loss correlated with seizure control at 3 months [43]. This was not seen in any other time point, with children or in any ketogenic diet study previously. Although still restrictive, the modified Atkins diet appears to work quickly, often within 2 weeks when effective.

A study from Massachusetts General Hospital in 2005 described an even less restrictive diet, the 'low glycaemic index treatment' [46]. This diet restricts carbohydrates to 40–60 g/day, does not restrict fluids or protein, but loosely monitors fat and calories. Unlike the modified Atkins diet, the type of carbohydrates is important in this diet, with only carbohydrates with glycaemic indexes <50 allowed. These carbohydrates include berries and wholegrain breads as opposed to potatoes, white bread and most citrus fruits. Efficacy is also surprisingly good despite an absence of urinary and only low levels of serum ketones [46].

Further studies in both children and adults of both diets are under way. Unanswered questions include long-term efficacy, comparative efficacy versus the ketogenic diet and the use of these diets for new-onset seizures. Both diets may also be of value in developing countries without dietitian resources but with large numbers of children with intractable epilepsy.

Indications for the ketogenic diet

The use of the ketogenic diet is restricted mainly to the treatment of refractory paediatric epilepsies (Table 23.1). There is no question that children who have cognitive or behavioural side-effects from multiple anticonvulsants can show improvement on the ketogenic diet in combination with a reduction in medications [39]. In addition, the ability to exercise control over their child's epilepsy makes the ketogenic diet attractive to many parents [39]. Children with gastrostomy tubes is also a population that is likely to be compliant with improved efficacy over children with solid-food ketogenic diets [47,48]. Some important contraindications to the ketogenic diet are listed in Table 23.1.

Many researchers have sought to identify predictive factors for maximal benefit from the ketogenic diet. Age of the child does not seem to be a factor in predicting effectiveness, with several studies showing no difference in outcome [15,16]. Certainly, infants can tolerate and derive significant benefit from the ketogenic diet if followed carefully [49]. Infants can do extremely well,

Table 23.1 Indications and contraindications of the ketogenic diet.

Indications
Intractable epilepsy (children)
Epilepsy with intolerable anticonvulsant side-effects
Glucose transporter protein deficiency (GLUT1)
Pyruvate decarboxylase deficiency
Suggested indications
Infantile spasms
Myoclonic–astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett's syndrome
Severe myoclonic epilepsy of infancy (Dravet's syndrome)
Formula-fed infants
Gastrostomy tube-fed children
Certain mitochondrial disorders
Contraindications
Pyruvate carboxylase deficiency
Porphyria
Carnitine deficiency (primary)
Fatty acid oxidation defects

especially as the diet can be provided as a liquid formula using Ross Carbohydrate Free (RCF) formula, Microlipid and polycose. In addition, a commercially available, powder formula, ketogenic diet (KetoCal) is available in premixed 3:1 and 4:1 ratios (Nutricia, North America, and SHS International, Liverpool, UK).

Seizure type and EEG pattern also do not seem to be predictive [15–17]. In the multicentre trial [15], there was no difference in outcome between seizure types, although a small decrease in efficacy was seen for those children with multifocal spikes on EEG at 3 months ($P = 0.04$). A common conception is that children with Lennox–Gastaut-type seizure disorders will have better improvement on the ketogenic diet, but at least one study looking at that issue found no statistically significant difference [16]. Seizure frequency also has not been shown to be predictive [16].

Special indications for the ketogenic diet do exist in paediatric epilepsy. Children with glucose transporter protein deficiency (GLUT1) and pyruvate dehydrogenase deficiency should be treated with the ketogenic diet as first line [50,51]. In both cases, the utilization of alternative sources to glucose for brain metabolism can prevent seizures by providing acetyl CoA directly into the tricarboxylic acid cycle without prior glycolysis.

There are other epilepsy syndromes that appear to respond preferentially to the ketogenic diet. A retrospective study of 23 infants placed on the ketogenic diet for difficult-to-control infantile spasms revealed 38% with greater than 90% seizure reduction at 3 months and 46% at 12 months with greater than 90% seizure reduction [52]. Of these infants, 57% had their medications reduced and the same number had developmental progression, which was correlated with seizure control ($P = 0.03$). Even in this age range, in which some children were as young as 5 months, tolerability was high.

The next logical study, considering the evidence for preferential benefit towards infantile spasms, was recently published in 2008 [53]. In this study, the first specifically of its kind, the ketogenic diet was used as a first-line therapy for infantile spasms. The diet was successful within days in 62% (8 of 13), whereas adrenocorticotropic hormone (ACTH) was of benefit in 90% (18 of 20; $P = 0.06$). In those in whom diet was not able to stop their spasms typically within 2 weeks, other therapies, including ACTH, were helpful in the majority immediately afterwards. Side-effects and the recurrence rate were lower with the ketogenic diet [53].

Other epilepsy conditions that do well on the ketogenic diet include myoclonic–astatic epilepsy (Doose syndrome) [54] and tuberous sclerosis complex [55]. These conditions may also be reasonable to consider for 'early', perhaps first- or second-line therapy, with parental consent.

Calculation of the ketogenic diet

The ketogenic diet is calculated individually for each child; however, there are certain guidelines for deciding on the ratio, calories and fluid requirements. The ratio of fats to carbohydrates and protein is based on the age, size, weight and activity level of the patient. Infants, children younger than 2 years of age and adolescents often receive a 3:1 diet to provide additional protein for growth and increased carbohydrates to improve compliance. Children aged 2–12 will typically be started on a 4:1 diet. During the fine-tuning of the diet to achieve greater efficacy, children may be given anything from a 2.5 to 4.5:1 ratio. Research suggests that a 4:1 ketogenic diet may be more effective; however, a 3:1 diet is better tolerated and is associated with fewer gastrointestinal symptoms [56].

Calories have historically been restricted to 75% of the recommended daily intake for age, but there is little research that supports the need to restrict calories or fluid to achieve seizure control with the ketogenic diet. At our institution, calories are estimated individually, taking into account a 3-day diet record provided by the parents. In addition, anthropometric data including weight for age, height for age, and weight for height or body mass index (BMI) are evaluated, as well as estimated ideal body weights, dietary reference intakes (DRIs), gender, age, activity level and other medical conditions and medications that may alter metabolism. Significantly overweight children may be given only 25–30% of the recommended calories until they approach their ideal body weight; however, a retrospective review of 123 patients found no association between ideal BMI or changes in BMI and efficacy of the ketogenic diet for seizure control [57]. The goal is to provide adequate calories and protein to promote growth along the patient's curve on his or her growth chart. Computer-generated meals are created individually, taking into account the child's food preferences, to increase tolerability.

Fluids are restricted to caffeine- and carbohydrate-free beverages at 80–100% of estimated daily needs. Fluids are unrestricted in children with a family history of renal calculi, infants and all children during times of acute illness. Parents are encouraged to check their child's urine specific gravity weekly to assess the adequacy of fluid provision.

Initiation of the ketogenic diet

Children are fasted for 24 h prior to the initiation of the diet, beginning after the dinner on the day prior to admission. Occasionally, medically complex children will not be fasted (Table 23.2). There are many centres now that do not fast children, and research indicates that there is no difference in efficacy between fasted and non-fasted children [58]; however, the more rapid reduction of seizures that can be seen with earlier ketosis is often very reassuring for family members [59,60].

On day 1 of hospitalization, the child is admitted during the 24-h fast. Fluid intake is encouraged due to the effects of ketosis on thirst. Blood glucose is monitored with finger dextrosticks every 6 h, unless it falls below 40 mg/dL, after which it is checked every 2 h. If the child has symptoms of hypoglycaemia, or the glucose level falls below 25 mg/dL, 30 mL of orange juice is provided and the glucose is checked 1 h later. Even small children tolerate the fast well, with rare symptomatic hypoglycaemia. Daily urine ketones are also checked. Ketosis can begin during the fasting period, and the resultant nausea and vomiting can occasionally require intravenous hydration using non-dextrose-containing fluids.

Anticonvulsant medications are often continued during the fasting and initiation period at their previous doses. All medications are carefully examined for carbohydrate content and

Table 23.2 Ketogenic diet protocol at Johns Hopkins Hospital.

Day prior to admission (Sunday)
Fasting starts the night before admission
Day 1 (Monday)
Admitted to the hospital
Fasting continues until dinner (24 h)
Fluids restricted to 80–100% of estimated needs
Blood glucose monitored every 6 h
Use carbohydrate-free medications when possible
Dinner given as one-third of calculated diet meal as eggnog or ketogenic formula
Parents begin education programme
Day 2 (Tuesday)
Breakfast and lunch given as one-third of diet as eggnog or ketogenic formula
Blood glucose checks discontinued after lunch, if lunch tolerated
Dinner given as two-thirds of calculated diet meal as eggnog or ketogenic formula
Education continues
Day 3 (Wednesday)
Breakfast and lunch given as two-thirds of diet as eggnog or ketogenic formula
Dinner increased to full ketogenic meal (not eggnog)
Education continues
Day 4 (Thursday)
Full ketogenic diet breakfast and lunch given
Education completed
Prescriptions provided for carbohydrate-free anticonvulsants and supplements
Child discharged to home

Table 23.3 Typical day of food for a child on a 4:1 ratio, 1500-calorie ketogenic diet.

Breakfast: eggs with bacon
Egg (28 g)
Cooked bacon (11 g)
36% heavy whipping cream (37 g)
Butter (23 g)
Apple (9 g)
Snack: peanut butter ball
Peanut butter (6 g)
Butter (9 g)
Lunch: tuna salad
Tuna fish (28 g)
Mayonnaise (30 g)
Celery (10 g)
36% heavy whipping cream (36 g)
Lettuce (15 g)
Snack: keto yoghurt
36% heavy whipping cream (18 g)
Sour cream (17 g)
Strawberries (4 g)
Artificial sweetener
Dinner: cheeseburger
Ground beef (22 g)
American cheese (10 g)
Butter (26 g)
Cream (38 g)
Lettuce (10 g)
Green beans (11 g)
Snack: keto custard
36% heavy whipping cream (25 g)
Egg (9 g)
Pure vanilla flavouring

formulations changed when necessary. There is no evidence that anticonvulsant serum levels are altered by ketosis [61].

Fasting continues until dinner on day 1 of the admission, when one-third of the calculated diet is provided as an 'eggnog' or ketogenic formula. A ketogenic eggnog looks and tastes like a milkshake and can be sipped, frozen as ice cream or cooked as scrambled eggs. Excess ketosis at this time, which causes nausea and vomiting, can be relieved with a small amount of orange juice. Once the child begins eating, serum glucose checks are unnecessary and are discontinued.

Breakfast and lunch remain at one-third of the calculated calories as eggnog or formula on day 2, but dinner increases to two-thirds of the usual allowance (still eggnog or formula). On day 3, breakfast and lunch are also increased to two-thirds of allowance, and dinner is then given as the first full ketogenic diet meal (with actual foods provided). On hospital day 4, the child receives a full ketogenic breakfast and lunch and is discharged to home. All children are sent home with prescriptions for urine ketosticks, additional calcium and a sugar-free, fat-soluble vitamin and mineral supplement.

Throughout the 4-day hospital stay at our institution, classes are held with physicians, nurses and dietitians to teach the family about the rationale of the ketogenic diet, calculation of meals, nutrition label reading and management of their children during illnesses. This is just as important to achieving a favourable outcome as the actual logistics of the diet initiation. Examples of typical ketogenic meals are given in Table 23.3.

After discharge, parents are instructed to check urine ketones daily, and the diet is individually adjusted after consultation by telephone or email to maximize seizure control. Another option is to use commercially available blood ketone meters that measure β-hydroxybutyrate levels (range 0–4 mmol/L). The advantages of these meters over urine ketones remains to be determined, but in some cases the urine ketones may measure 'large' (the highest level on urine ketone sticks) at the same time that serum ketones will only be 2 mmol/L. In some cases, additional seizure control was potentially gained when ketosis was pushed higher, to achieve a serum ketone level above 4 mmol/L [62]. Most ketogenic diet centres do not advocate the routine measurement of serum ketones using these meters, however, as the evidence of direct correlation of efficacy to any measure of ketosis remains controversial today.

Serum glucose or electrolytes are not routinely monitored after discharge. Weight is monitored by the parents and reported if significantly changed. Periodic laboratory measures are obtained typically every 3 months in order to monitor for side-effects (lipid profile, electrolytes, anticonvulsant levels, urine calcium/creatinine). Urine alkalinization is accomplished with the use of Polycitra-K for all patients if the urine calcium to creatinine ratio is elevated above 0.2. However, as the use of Polycitra-K resulted

in a threefold reduction in kidney stones, we now currently advocate its empiric use for all children at our centre [63]. Medications may be tapered and discontinued on an individual basis, as one of the most common parental reasons for starting the diet is anticonvulsant reduction. As evidence suggests that it is safe to wean anticonvulsants even during the first 1–2 weeks of the ketogenic diet [64], this goal should be discussed with each family [40]. Children should be seen in clinic every 3 months, with more frequent visits for infants and medically fragile patients.

Handling increased seizures

Parents and physicians not familiar with the ketogenic diet are often very uncomfortable handling increased seizures. Certain basic management options apply to help improve seizure control. Parents are instructed to maintain seizure calendars that include daily ketone levels, medication changes, illness, diet/food changes or other activities that may affect seizure control. First, we always try to ensure that no new medications have been added that might contain carbohydrate (e.g. antibiotics, anticonvulsants). Occasionally, topical ointments and lotions (e.g. sunscreen, hair gels) contain sorbitol, which can be systemically absorbed, especially in very young children. Many food additives are described as 'sugar free' but contain carbohydrate-containing chemicals such as maltodextrin, sorbitol, starch and fructose. Secondly, the family should check urine ketones to ensure adequate ketosis. If ketones are not moderate to large, the child can be fasted with clear liquids for 24 h to improve ketosis rapidly. If there is no known aetiology of increased seizures, carnitine and/or MCT oil may be added. Carnitine is a carrier of fatty acids into the mitochondria for fatty acid oxidation and, although not necessary as a ketogenic diet supplement, serum levels often are reduced with ketogenic diet therapy [65]. MCT oil is more ketogenic than the LCTs that make up the classical ketogenic diet, and is more easily absorbed and transported into the cell than LCTs. Periodic oral or rectal benzodiazepines can be useful for seizure exacerbations as well.

Discontinuation of the ketogenic diet

The issue of when to discontinue the ketogenic diet is a difficult one. In children who are doing well, many parents are appropriately reluctant to discontinue a therapy that has been effective for years and risk restarting the anticonvulsants that were either ineffective in the past or caused side-effects. Because of the potential long-term adverse effects of the diet on lipids and growth, after 2–3 years on the diet there is a temptation to try to discontinue it, recognizing that it can always be restarted if necessary. Evidence suggests that a recent epileptiform EEG, structural brain abnormality on magnetic resonance imaging (MRI) and presence of tuberous sclerosis complex increase the risk of recurrence in seizure-free children who then discontinue the ketogenic diet [66]. As with anticonvulsants, when discontinued it is usual to taper the diet slowly over 2–3 months by gradually lowering the ratio of fat to protein and carbohydrate, then relaxing the weighing of ingredients and, finally, adding new carbohydrate foods over weeks while keeping calories constant.

A recent study of children who discontinued the diet prior to 1 year, in most situations due to inefficacy, determined very surprisingly that nearly 50% of these children had less than half of the seizures they had before starting the diet 3–6 years previously [67]. Several of these children had epilepsy surgery or vagus nerve stimulation implantation, yet even those who did not had a long-term prognosis that was much better than would be expected considering their intractable epilepsy (even to the ketogenic diet). This evidence, although very limited, suggests that the ketogenic diet may be not only anticonvulsant in the acute setting, but anti-*epileptogenic* in the long term. Further studies are under way.

The timing of dietary discontinuation in the child with no perceived seizure reduction has been investigated recently. Nearly 90% of children who improve on the ketogenic diet do so within 1 month, and nearly all by 2 months [36]. Therefore, continuing the ketogenic diet beyond 6 months in a child with no seizure improvement would seem inappropriate. Typically, if a child has been on the ketogenic diet for only several months, he/she can be weaned over 2–3 weeks. If the child is having significant difficulty with the ketogenic diet, he/she can be discontinued immediately, however, without dramatic increase in seizures in most cases.

Side-effects

The ketogenic diet is not without side-effects. As with any medical therapy for seizures, benefits need to be balanced against risks (Table 23.4). Side-effects were recently well summarized in an editorial by Wheless [68].

During the initiation of the ketogenic diet, the fast itself can cause vomiting, dehydration and food refusal. These effects are usually transitory and easily treated; however, if the child has an underlying metabolic disorder, the fast and ketogenic diet can be dangerous. All children, especially infants, need to have a thorough history, physical examination and often screening tests (lactate, pyruvate, carnitine, electrolytes, urine organic acids and serum amino acids) performed prior to initiating the diet. Diseases that could potentially deteriorate on the ketogenic diet include pyruvate carboxylase deficiency, porphyria, primary carnitine deficiency, certain mitochondrial disorders and fatty acid oxidation defects (see Table 23.1) [65].

Some of the more common side-effects include constipation, exacerbation of gastro-oesophageal reflux, acidosis with illnesses,

Table 23.4 Side-effects reported with the ketogenic diet.

Constipation
Exacerbation of gastro-oesophageal reflux
Water-soluble vitamin deficiency (if unsupplemented)
Elevated serum cholesterol, triglycerides, and low-density lipoprotein cholesterol
Renal stones
Growth inhibition
Weight loss
Worsening of acidosis with illnesses
Bone fractures
Vitamin D and selenium deficiency
Cardiomyopathy

growth difficulties, renal stones and hyperlipidaemia. Constipation and gastro-oesophageal reflux disease are common and likely to be secondary to the low-roughage and high-fat component of the ketogenic diet. Both can be treated effectively with increased fluids, stool softeners and laxatives when necessary. The use of MCT oil in the diet can often be helpful for constipation also. Acidosis, not only during the initiation of the diet but also during acute illnesses, is a true concern and needs to be discussed at length with the family. At the time of diet initiation, parents should be taught the signs of acidosis and how to hydrate with non-sugar-containing fluids.

Growth is often of concern for parents, and they need to understand that weight gain may be reduced with the ketogenic diet. A recent review of the diet in 237 children revealed a reduction in the rate of weight gain (more so in children above the average median weight) at 3 months but which then remained constant for up to 3 years [69]. The rate of increase of height remained normal for the first 6 months of the diet but then decreased over the next 18 months, especially in those children above the median to start. There were also significant differences between age groups for height and weight, with younger children growing less well.

Renal stones occur in approximately 6% of patients and tend to be either uric acid or calcium oxalate stones [70–72]. Children with a family history of kidney stones (even calcium stones) may be at higher risk for renal calculi and should be hydrated more aggressively and their urine alkalinized [72]. Renal ultrasound should be performed in any child with haematuria or pain upon urination. Periodic spot urine calcium to creatinine ratios can also help screen for this condition. If the ratio is >0.2, potassium citrate should be started to help alkalinize the urine in children [63]. Lithotripsy, or occasionally surgical removal, can be performed successfully and the diet continued, and renal stones should not be considered a mandatory reason for withdrawal of the diet. Recent evidence suggests that potassium citrate reduces the risk of kidney stones threefold, and we now routinely start all children on this supplement at diet initiation [63]. Although there does not appear to be a higher risk of stones with combination use of topiramate or zonisamide, we suggest that if these drugs are being used in a child on the ketogenic diet, they should be stopped [72].

Hypercholesterolaemia does occur on the ketogenic diet. Sixty per cent of children will have abnormal cholesterol or triglycerides during their treatment with the diet [73]. Abnormal results are less likely in children receiving a formula-only ketogenic diet [74]. The increase in cholesterol may be due to a ketogenic diet-induced decrease in apolipoprotein B (apo B), the major serum carrier of cholesterol [73]. Triglycerides also increased in this study, but then later normalized. The long-term effects of the ketogenic diet on atherosclerosis remain to be determined; however, most children on the ketogenic diet for 6–12 years in one cohort had normal or only slightly elevated total cholesterol and triglycerides [75]. Adjustments to the diet such as additional MCT oil or polyunsaturated fats and decreased ketogenic ratios can be made in children with significantly elevated triglycerides and cholesterol, and were successful 60% of the time [74]. Children should be screened with a serum cholesterol level if physical examination findings (such as cholesterol deposits in skin or retina) or a family history of early atherosclerosis indicates the possibility of familial hypercholesterolaemia.

More uncommon complications attributed in the literature to the diet have been reported [76–79]. They include cardiomyopathy, pancreatitis, bruising and vitamin deficiency. Most were case reports and do not prove that these problems were diet related. Four of five patients reported by Ballaban-Gil [76] had severe hypoproteinaemia, Fanconi's renal tubular acidosis and increased liver function tests potentially in combination with valproate. The correlation of these complications with the ketogenic diet is unclear, but the authors propose a possible additive effect with valproate interfering with carnitine function and fatty acid oxidation. In a study by Best *et al.* [77], prolonged QT interval was discovered in 3 of 20 patients, but this has not been reported elsewhere. No child at our institution has ever had arrhythmias or cardiomyopathy attributable to the ketogenic diet. Increased tendency for bruising was seen in a recent study in 16 of 51 children reported by Berry-Kravis *et al.* [78]. Vitamin deficiency is rare [80]; however, it can be appropriately avoided using supplementation. Routine administration of magnesium, selenium, zinc, vitamin D, vitamin C, B-complex vitamins and additional calcium is recommended.

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24 Non-pharmacological, Complementary and Alternative Treatments for Epilepsy

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Most general reviews of treatment for epilepsy concentrate entirely on the pharmacological agents on offer. Most of the rest of this book demonstrates this. When non-pharmacological treatments are discussed, these include, almost without exception, only surgical interventions, vagus nerve stimulation and the ketogenic diet. This chapter is concerned with other treatments which have been tried, or which might usefully be further investigated and which continue to be used by a large number of people with epilepsy. One survey of all members of the Epilepsy Federation of Arizona found that 44% had used a non-conventional treatment for their seizures at some time [1]. The authors extrapolated their results and found that, of 24 000 individuals with epilepsy (IWE) in Arizona, probably 10 500 were using or had tried a non-conventional therapy for their seizures. An interesting difference in studies of complementary and alternative medicine (CAM) in general is in the proportion of individuals with epilepsy who avoid telling their physicians about CAM use. In this survey (2003), only 7% of 379 patients with epilepsy said that they would not tell their physician about CAM use. Earlier surveys suggested that up to 40% of people using CAM in the general population omitted to tell their physicians of the use [2]. A more recent survey [3] of 228 IWE in the western USA found that 39% reported using some form of CAM, with 25% reporting use specifically for epilepsy. These studies do bring up the issue of lumping all non-conventional treatments into one category, as if, for example, prayer as a form of CAM is to be considered as in some way similar to acupuncture, which is clearly true only if they are both just considered as 'non-conventional'. The rising tide of concern among patients in the Western world about the side-effects of conventional pharmaceuticals has been considered one reason for the rapid rise in popularity of many forms of unconventional medicine [4]. Nowhere is this concern more likely to be felt than among sufferers of epilepsy, a predominantly youthful population which has to take such agents daily for many years, and their families. Any techniques or treatments which could be applied to reduce the need for conventional medication, in even a small proportion of sufferers, are worth noting by all those who care for people with epilepsy.

Some of these techniques, such as EEG biofeedback, psychotherapy, relaxation and hypnosis, verge on the mainstream, but most of them are more commonly viewed under the CAM banner. CAM refers to 'diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy, or by diversifying the conceptual frameworks of medicine' [5]. As suggested earlier, there is an unfortunate tendency to lump all non-conventional practices together as 'alternative' and label them all as either 'good' or 'bad', depending on one's preference. Viewed more holistically, there are approaches on both sides of a notional dividing line which bring health benefits to particular individuals. There is little to guide us in knowing in advance which sufferers will benefit from which therapy. It is perhaps one of the tasks of medicine over the next few decades to integrate CAM therapies into treatment pathways, the prime goal being to alleviate suffering and promote health. Some such attempts are available as case reports [6,7]. Some are positive about possible developments in this direction [8] and some are worried [9,10]. It is notable that much of the concern appropriately springs from worries about the possible risks of forgoing conventional treatments (though most IWE use CAM as add-on, complementary therapy to their conventional management) and direct adverse effects of some CAM treatments [9,11]. Herbal interactions with AEDs are another major concern [10], but should be minimized if most IWE tell their physician what they are doing and if the physicians are at least a little knowledgeable about CAM.

This review aims to help answer the questions of what evidence is already available to help in the task of integration and what might be the most promising lines for future research to take.

Experience from the developing world suggests that people with epilepsy are extremely pragmatic in their approach to potential therapies, continuing to use anything which they perceive as helpful and quickly rejecting anything perceived as unhelpful. For example in a neurology outpatient setting in Lagos, Nigeria, it has been found that many people with epilepsy develop a personal care strategy which may combine elements of 'conventional' (pharmaceutical) and 'complementary' (traditional remedies and/or spiritual healing) medicine [12]. Similarly, this approach is widely adopted generally in the developed world [13]. There is, though, evidence of some improvement in public attitudes to epilepsy over time in many countries, and it is interesting to perform cross-cultural comparisons of treatment and perceptions of epilepsy between developed and developing countries. One study compared these factors in 28 IWE in the USA with 29 IWE in Kashmir [14]. Both samples had quite similar attitudes to

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AEDs, though the American group had a greater access to newer drugs and also to non-pharmacological treatments. The two groups both expressed frustration at the societal lack of understanding of their condition and the importance of support from family and friends. On the whole, both groups used alternative treatments in addition to, rather than instead of, conventional therapies, with spiritual practices and prayer being considered most important. A very well-told case of a child with severe generalized seizures born in California after the family had been forcibly resettled from IndoChina shows how important it is for Western-trained physicians to be sensitive to cultural differences in their patients [15]. Even in the UK, non-indigenous communities can maintain a strong belief that epilepsy is just the 'will of God' and 'punishment for sins of a past life' and turn to spiritual practices and traditional healers along with conventional treatment in a desperate search for a 'cure' [16]. These examples suggest that it is vital for those who care for people affected by epilepsy to have at least a basic familiarity with the more commonly used CAM treatments. This should enable appreciation of any safety issues, such as potential drug interactions, enhance the understanding relationship between health professional and patient and even allow the occasional referral for appropriate, effective non-conventional treatments.

There are a number of unconventional and CAM therapeutic approaches that are sometimes helpful in the treatment of epilepsy. There are some studies which help to indicate which individual patients might benefit, but as there has been relatively very little funding of research in CAM and there are few well-established research networks, case reports and individual clinical experience have a strong role. The rise of evidence-based medicine (EBM), and the risk of providers allowing funding only if a treatment comes up to some acceptable standard of EBM, is very much a concern in the CAM therapist community. Since the only acceptable 'evidence' seems to be that from randomized clinical trials and since not many CAM therapies are well supported by this kind of evidence, much of what follows may be felt unacceptable. Certainly, the amount of apparently quite good 'evidence' specifically excluded from Cochrane reviews (as the major publications in EBM) causes a worry that some effective treatments could be increasingly overlooked because they have not come up an evidence standard against which they have never been tried.

Therapies with varying levels of seeming evidence of efficacy in epilepsy include behavioural/psychological therapies such as psychotherapy, cognitive therapy, hypnosis, meditation, EEG biofeedback and relaxation, herbal medicine, low-antigen diets, dietary supplements, music therapy, exercise, homeopathy, acupuncture, transcranial magnetic stimulation and chiropractic therapy.

Psychological/behavioural treatments

Many different therapies which could come under the 'psychological' or 'behavioural' tags have been tried in epilepsy. Much of the literature reports single cases or very small studies, but there are Cochrane reviews of psychological treatments for epilepsy [17] and of behavioural treatments for non-epileptic seizures (NES) [18]. To an extent, these supersede the reviews of Fenwick [19] and Goldstein [20], but they are limited to detailed comment only about randomized controlled trials (RCTs) and some may find the more discursive and 'real life' clinically focused earlier discussions more useful, though Goldstein is a joint author of the Cochrane review. Ramaratnam *et al.* [17], therefore, have to dismiss most of the high-quality work that has been done over the years on EEG biofeedback or relaxation training, as adequate RCTs are not available. Similarly, Brooks *et al.* [18] are only able to include three trials, two of hypnosis and one of 'paradoxical therapy', in a discussion which aims to 'establish the evidence base for treating NES'. The conclusion, of course, has to be that there really is hardly any evidence on strict Cochrane criteria, but this does seem to be a process that takes attention away from possibly helpful treatments. The reader is directed to these authors for further detail, but, broadly, psychotherapy, individual counselling and cognitive behavioural therapy (CBT) may help the psychological problems associated with epilepsy, and there is a suggestion of reduction in seizure frequency with some of these techniques. Operant or classical conditioning is reported to decrease seizure frequency and to be particularly helpful in control of the reflex epilepsies (seizures reliably triggered by a specific sensory stimulus, such as music or strong smells). Cases have also been reported of the beneficial effect of changing arousal levels in response to cues indicative of the onset of a seizure. Such 'countermeasures' are individually designed, according to the seizure cues, and many patients soon discover what action is effective for them to abort a threatened seizure.

Hypnosis

Hypnosis is a technique by which general arousal levels can be changed. It has not been assessed unrelated to other therapies in RCTs, and this is discussed in the Cochrane review of treatment of non-epileptic seizures [18], though there are many case reports. One highly developed programme in an epilepsy centre combined it with aromatherapy and reported on its first 100 patients, concluding that for those individuals who are highly motivated, hypnosis plus aromatherapy had a very helpful, lasting effect [21]. A report on just two patients suggests that it can be effective in control of seizures [22]. An impressive case report gives great detail of the hypnotic processes learned by a woman with Jacksonian seizures due to a benign, but inoperable, frontotemporal tumour. She reduced her seizure frequency from 35 to five per week over the course of hypnotic treatment lasting 16 months [23]. Utility to distinguish 'psychogenic' [non-epileptic events (NEE)] seizures from epileptic events (EE) by the degree of 'hypnotizability' of the subject has been suggested. In one study [24], 60 patients attending a specialist epilepsy centre were evaluated. While undergoing continuous video-EEG monitoring, they completed an inventory designed to measure the degree of hypnotizability [the hypnotic induction profile (HIP)]. An attempt was made to induce the patient's typical events and any event without an EEG correlate was felt to represent an NEE. Results of the hypnotic assessment were compared with the diagnoses of NEE made independently by a neurology team. HIP scores for EE-only patients were significantly lower than for those who had NEE as some or all of their events. The sensitivity of seizure induction in the diagnosis of NEE was 77% and the specificity was 95%. The authors concluded that the HIP along with seizure induction

is a useful technique to aid in the diagnosis of patients with NEE.

Meditation and yoga

In a well-conducted study, 11 adults with drug-resistant epilepsy were taught meditation (of classical Indian word repetition, non-religious type) and followed up for a year of practice (20 min daily) [25]. They were compared with a waiting list control group of nine subjects, well matched for age, duration of illness and seizure type. Both groups received the same professional attention; the control group, however, did not practise meditation. The meditation group showed a reduction in attack frequency and duration after 6 months' practice compared with the 6-month period pretreatment, which became highly significant with a further 6 months' treatment. The meditators also demonstrated normalization of EEG recordings with prolonged treatment, with a reduction in mean spectral intensity of the 0.7–7.7 Hz segment and an increment in intensity of the 8–12 Hz segment. There were no changes in the controls. The authors discuss the rationale for the study in terms of eliciting the 'relaxation response' of Benson [26] and suggest that this might be a common link towards understanding the mode of action of all of these psychological techniques.

Yoga teaches a combination of physical postures, breathing exercises, relaxation and meditation to attain optimal physical and mental health. A number of documented clinical and physiological effects are relevant to epilepsy [27]. There are many different schools of yoga practice, some emphasizing control over the physical body, some control over the breathing and some specifically using meditative practices to calm the mind and achieve 'union of the individual energy ('prana') with the universal energy ('Brahman'). There are a number of methodological issues about the kind of yoga to be used and the diagnoses of participants which have to be overcome [28]. Most of the reports of yoga as treatment for epilepsy have been concerned with the directly meditative forms (specifically Sahaja yoga) and may perhaps be considered along with meditation as an intervention. A Cochrane review of yoga in epilepsy [29] identified five studies, but only considered data from one in detail. Interestingly, one of the excluded studies in this review of 'yoga' is that of meditation considered in detail above, and does not in fact mention yoga at all [25].

The study included by the Cochrane reviewers randomized 32 uncontrolled epileptic patients to three groups [30]. Group I (n = 10) was the yoga group, who practised Sahaja yoga meditation under guidance of an instructor twice daily for 20–30 min for the 6-month duration of the study. Group II (n = 10) practised mimicking exercises in the same environment as group I and were provided with the same attention. Group III (n = 12) was a control group, just being followed up in outpatients.

Four out of 10 patients in the active group became seizure free after 6 months of practice, compared with none out of 22 in the controls. Nine in the active group had more than a 50% reduction in seizure frequency compared with just one among the 22 controls. These differences are significant and suggest that further research in this area is justified, with larger group sizes.

A pilot open-label study of a yoga meditation protocol (YMP) has been performed at a specialist epilepsy centre in south India [31]. Twenty patients with epilepsy on maximal doses of standard antiepileptic drugs (AEDs) (age range 15–47 years, median 27 years) and at least four complex partial seizures in the preceding 3 months were asked to perform the YMP for 20 min twice daily for 3 months. They also attended for a supervised YMP session weekly. At 3 months, a reduction in seizure frequency to <50% of the pretreatment value was apparent in all except one patient. Of the 16 patients who (optionally) carried on the YMP beyond 3 months, 14 continued this response, as did all of the eight patients who elected to carry on for 6 months. Three of these became seizure free. The authors are recruiting for a RCT using sham yoga as a control.

Whether any changes are specific to a form of meditation called yogic, or indeed to any form of deep relaxation, and whether similar effects might be obtained with other, more familiar, physical forms of yoga remains to be elucidated.

It has been argued from a theoretical point of view that, as a rise in brain glutamate and serotonin and the development of 'hypersynchrony' of EEG activity which accompany meditative states are also known to underlie the development of epilepsy, so meditation might be expected to increase attacks in epileptics (a kindling phenomenon) [32]. This view of potential harm from meditating in epileptics has been strongly countered with clinical effectiveness and experiential arguments [33].

EEG and other biofeedback

Biofeedback in general involves the use of electronic displays to collect and show physiological processes to the patient, with the goal of increasing the patient's control over the internal processes and changing them at will. It has been extensively studied in a variety of neurological conditions. For example, thermal biofeedback (in which control of the skin temperature of a finger is learned) and electromyograph (EMG) biofeedback (in which control is learned over the tension in a muscle, such as temporalis) are well established as treatments for migraine and tension-type headache respectively, at least in the USA [34,35]. In EEG biofeedback, also referred to as EEG operant conditioning or neurotherapy, the subject learns to voluntarily control a chosen EEG rhythm which has been associated with suppressing seizure activity and thereby gain control over the seizures themselves. Initial work was done on the 'sensory-motor rhythm' (SMR) over the somato-sensory cortex, and it is this rhythm which has been most studied. Modern protocols use well-developed software with visual displays guided by quantitative EEG analysis. Biofeedback reinforcement of other rhythms such as the alpha rhythm and also the suppression of slow wave and spike activity have also been investigated and found to be effective in some studies. There is much debate in the literature about just which rhythms are likely to be most useful for biofeedback for which conditions.

Sterman and Friar first observed protection against drug-induced seizures in cats following operant conditioning of 11–15 Hz sensorimotor EEG rhythm to produce a sustained increase in the rhythm. They used the technique to successfully treat a 23-year-old woman with a 7-year history of generalized major tonic–clonic seizures of unknown origin, occurring at least twice monthly. The seizures had proved resistant to many drug regimes. With 3 months of twice-weekly biofeedback training enhancing 11–15 Hz activity, she became seizure free [36].

In a comprehensive review of the literature from the first case report in 1972 to 1996, Sterman [37] collected the results on a total of 174 patients with intractable epilepsy treated with sensorimotor EEG operant conditioning, in 18 studies from many different authors. One hundred and forty-two (82%) of those who were otherwise not controlled showed 'clinical improvement', that is reductions in seizure frequency of at least 50%. The average value of reduction of seizure frequency was above 50% and many of the studies reported reductions in seizure severity. Approximately 5% of this difficult subset of epileptic patients experienced complete control of seizures for up to 1 year. Not all studies reported EEG findings, but of those that did, 66% of reported cases (in 13 studies) showed 'EEG improvement'. Most of the studies are of very small groups of under 10 patients and many of them report individual patient characteristics and outcomes, often using the patients as their own controls in pre- versus post-treatment comparisons of frequency and severity. Two larger studies [38,39] report on groups of 23 and 83 patients and find significant beneficial effects on seizure frequency.

Sterman [37] comments that 'the consensus arising (from the studies) is that most epileptic patients who show clinical improvement with EEG biofeedback also show contingency-related EEG changes and a shift towards EEG normalization. However, not all patients who respond to this treatment show EEG changes and a few patients who show EEG changes experience little clinical improvement. In a further, very comprehensive, review of principles underlying neurofeedback [40], he tells us that it is now so well documented that it meets criteria in seizure disorder for 'clinical guidelines' of evidence-based treatments of the American Academy of Child and Adolescent Psychiatry. It is reassuring to read of groups other than the originators publishing experience of this technique [41].

Advocates of EEG biofeedback point to an accumulation of evidence of positive effects in neurophysiological and clinical studies over the past 25 years. They lament the lack of interest in its potential usefulness for a most difficult-to-help group of patients in the wider neurological community and specifically that the technique is still regarded as 'experimental' [37]. Sceptics may acknowledge that there are 'adequate data to suggest that EEG biofeedback can work in some clinical conditions' [42], but clearly, a lot more work needs to be done to satisfy the demands of non-enthusiasts before EEG biofeedback can take its place as a generally available option for people with intractable seizures. For the individual strong-responding patients who have been able to come off all anticonvulsants and return to work [43] or be issued with a driving licence for the first time [36], this view may seem a little narrow.

It is undoubtedly a rather lengthy and expensive treatment in terms of laboratory, technician and patient time, and there is as yet no way of determining in advance which patients will benefit.

One study with skin galvanic biofeedback is considered in the Cochrane review of psychological treatments [44]. This is, of course, a much less complicated procedure than EEG biofeedback. Eighteen patients were randomized to receive either active or placebo skin galvanic skin response biofeedback for three sessions per week for 4 weeks. Seizure frequency was compared in the 3 months before the treatment with the 3 months afterwards. All had AED-refractory epilepsy. Six of 10 in the treatment group had 50% or greater reduction in seizure frequency compared with none of eight in the sham feedback group.

Relaxation

Relaxation has been investigated as a possible treatment for epilepsy in at least four controlled studies. The particular form of relaxation generally used has been progressive muscular relaxation (PMR), as codified by Bernstein and Borkovec [45]. An early report was that of Snyder [46], who recruited 16 patients with mostly 'mixed' seizures. Only four practised relaxation on 15 or more days each month, but of these three reported a decrease in seizure frequency. Rousseau and colleagues performed a controlled study [47] and placed eight subjects into two groups on a sequential, alternating basis. Group I underwent a training session in PMR and were then asked to practise the exercise twice daily for the next 3 weeks. Group II were initially trained in a sham treatment and sat quietly for 20 min twice daily, relaxing as best as they could. Baseline seizure frequency was recorded for the 3 weeks before training and both groups continued to record seizure frequency through the first 3 weeks of the study. At the end of 3 weeks, group II was taught PMR and practised twice daily for the next 3 weeks, recording seizure frequency. There was a significant decrease in seizure frequency after PMR training (by 43–100%) compared with after the sham (0–51%), although two subjects also did well with the sham.

Whitman *et al*. [48] trained 12 patients in PMR who had at least six seizures in an 8-week baseline period and followed them up for 6 months, but did not include a control group. The mean reduction from baseline in seizure frequency at 6 months was 54%. Puskarich *et al*. [49] enrolled 24 subjects with at least six seizures in a baseline period of 8 weeks. They were randomized in alternating blocks of five to a group which received six sessions of training in PMR ($n = 13$) and a control 'quiet sitting' (QS) group ($n = 11$) which attended six times for 30 min of non-directive conversation, followed by 15 min of sitting alone in a reclining chair in a darkened room. This training period lasted 8 weeks. The groups were then followed up for 8 weeks. In the PMR group, 11 subjects had a decreased frequency of seizures from baseline to follow-up ($P < 0.01$), and in the QS group seven had a decrease ($P < 0.05$). The mean decrease in seizure frequency was 29% (from 17.0 at baseline to 12.1 during follow-up) for the PMR group and 3% for the QS group (from 10.3 at baseline to 10.0 during follow-up). Subject numbers and study quality have risen with each new report and there is increasing evidence for a worthwhile effect on seizure frequency of this simple psychological intervention.

There is also evidence that adults with resistant seizures can learn early signs of cortical dysarrhythmias and apply relaxation acutely to inhibit the seizure [50].

Psychiatric interventions

One study reviewed experience with 37 patients with uncontrolled seizures, whose seizures seemed to be precipitated by emotional stress [51]. Each received psychiatric intervention on at least two occasions (range 2–70, median 7.5). The intervention consisted of 'individual and family assessment, followed by the formulation of a treatment strategy geared toward alleviating

possible psychogenic contributions to the patient's seizures'. It should be noted that in an appreciable proportion of these cases, 'hysterical' seizures were rated as being probably (19 of 37) or definitely (3 of 37) present. After 2–36 months' follow-up (median = 6.5 months), 9 of 37 patients became seizure free and 12 additional patients showed a marked improvement (at least two-thirds decrease in seizure frequency). Patients with partial seizures were more likely to respond than those with generalized seizures, and those with non-epileptic ('hysterical') seizures were especially responsive. Hypnotizability and having an intelligence quotient (IQ) within the average range were also positively associated with a favourable outcome.

An analysis of 70 case studies in psychological approaches for prevention of nocturnal seizures encompasses extremely heterogeneous groups of patients and treatments [52]. Its author is unable to draw any firm conclusions, specifically about factors which might predict good response to a particular therapy. Most provocatively, it is suggested that freedom from seizures as a consequence of psychological treatment of epilepsy was most often achieved in these 70 cases when AEDs were withdrawn.

In conclusion, there are a number of psychological/behavioural interventions which have been well studied and considered to be helpful as additional therapy for even the most drug-resistant epileptic patients. Choice of intervention probably depends mostly on local availability and patient preference and motivation, as there are, as yet, few indications of which technique is most likely to be helpful in an individual.

Exercise

There has been a reluctance to allow normal participation by epileptic patients in physical activity and sport, generally due to fear of injury or concern about exercise-induced seizures, although there has generally been a shift in medical opinion away from restricting participation towards encouragement. There appears to be no generalized increase in seizure frequency with physical exercise [53], although there is considerable individual variation. Exercise has been studied as a possible means of reducing seizures in drug-resistant epilepsy. Eriksen *et al.* [54] gave 15 women with drug-resistant epilepsy (median 2.9 seizures per week) physical exercise sessions twice per week for 15 weeks. The exercise sessions lasted 1 h and consisted of a warm-up, 30 min of aerobic dancing, a cool-down, 15 min strength training and 5 min relaxation, all accompanied by music. Seven subjects had a total of 27 seizures during the 30 exercise sessions, mostly during the aerobic dancing or cool-down periods. Self-reported seizure rate was significantly reduced during the 15 weeks of the intervention (from 2.9 seizures/week at baseline to 1.7/week during exercise) and there was also a reduced level of other health complaints, such as muscle pains, sleep problems and fatigue. The positive effects did not, however, last through a follow-up period of 3 months, when most subjects were unable to continue exercise on their own. The authors feel that 15 weeks is not long enough to effect a complete lifestyle change towards regular, hard physical activity. They believe that the benefits of increased fitness, decreased overall health complaints and reduction in total number of seizures more than balance the relatively few seizures during exercise that occurred in half of the subjects. Accordingly, they recommend that physical activity such as aerobic dance can be recommended to epileptic patients, its most important effect being 'the normalization of the life situation for severely affected hypoactive and understimulated epileptic patients'.

Music

That music and different neurological diseases are in some way interconnected in human behaviour has long been appreciated (for a fascinating discourse, see Kaplan [55]). The specific entity of seizures being triggered by music (musicogenic epilepsy) is well recognized, but can it work 'the other way round' – can music be used to treat epilepsy?

The 'Mozart effect' was first reported as an enhancement of spatiotemporal reasoning after listening to Mozart's sonata for two pianos (K448) for 10 min [56]. Later, EEG changes such as enhanced synchrony of the firing pattern of the right frontal and left temporoparietal areas, persisting for 12 min, were demonstrated. In 23 of 29 epileptic patients with focal discharges, there was a significant normalization of the EEG after listening to Mozart's music and one case report describes an 8-year-old girl with Lennox–Gastaut syndrome and intractable, frequent seizures (about two per hour) who achieved a very significant reduction in attacks by the playing of the Mozart sonata for 10 min each hour of her waking time. These studies, and the probability that this effect is not specific to Mozart's music, are considered by Jenkins [57]. A more recent case of gelastic epilepsy in a 56-year-old man responded almost completely to listening to Mozart (not a specific piece of music) for an average of 45 min/day [58]. He had had gelastic fits since shortly after birth and developed tonic–clonic seizures during his mid-thirties. He was found on MRI to have a right hypothalamic hamartoma. He had tried seven AEDs, had Gamma Knife surgery and brachytherapy to the hamartoma, but the seizures did not change in frequency in the long term. Before he began listening to Mozart (which he did spontaneously as he had heard that it might enhance spatiotemporal reasoning) he was having gelastic seizures with intense laughter five or six times each day, as well as secondarily generalized tonic–clonic seizures on average seven times per month. In the 3 months after starting to listen to Mozart regularly, he had no secondary generalized tonic–clonic seizures. He continued to have five gelastic seizures a day, but these showed themselves as just brief, 5–9-s smiles, which could be disguised in the presence of others. The authors felt that 'it would be appropriate to revisit the Mozart effect in those with epilepsy'. It is hard to disagree.

The effect of another form of music – 'medical resonance therapy music' – has been studied in 34 patients in an epilepsy hospital in Minsk, Belarus [59]. This a commercial product (you can buy the CD) of 'harmonic music' by German composer Peter Heubner, which has been available as a 'stress reducer' for 19 years and has been used medically in migraine and other disorders thought of as 'stress related'. Subjects listened to the music daily for 1 h for 6 to 16 sessions. The author claims a 75% reduction in seizure frequency and a significant improvement in psychological state. Unfortunately, the report is very unclear, with no actual numbers of seizures given, only percentage improvements on

undefined scales. The kind of music is not well described, but appears to be a rhythmical, computer-generated creation, designed for therapeutic purposes rather than to be listened to for pleasure. Since there are no formal studies of more conventional music (Mozart K448, for example) with which it can be compared, this study stands as the only one of its type in epilepsy. The field looks ripe for experimentation.

Herbal medicine

A large number of plants are traditionally used throughout the world for the treatment of epilepsy. One review of the literature found around 150 plants or other natural substances from traditional medicines which have been tested for their *in vivo/in vitro* anticonvulsant activities in the last 30 years [60]. The authors felt that 10 of these warrant further study. It should be remembered that many herbal preparations of course have very significant interactions with commonly prescribed conventional drugs [10,61] or may cause seizures as side-effects [62], and use of these preparations should always be specifically enquired about.

One herbal mixture which has been quite extensively studied and which is sometimes recommended as add-on treatment for epilepsy is the Japanese mixture Saiko-keishi-to (SK). This is made up of parts of nine plants. Two other very similar mixtures have been studied, sho-saiko-to and the Chinese chai-hu-keui-chi-tang. These differ only in the relative amounts of the baseline herbs and they all appear to have equivalent effects. One study gave SK to 24 poorly controlled epileptic patients daily for at least 10 months, as add-on treatment, keeping the conventional AED regimes constant. Six became seizure free and 13 improved in seizure frequency or severity [63].

Another study found a greater than 25% reduction in seizure numbers in 8 of 24 patients with drug-resistant partial epilepsy after 8 weeks' daily treatment with SK. There were corresponding cognitive improvements [64]. Neither of these studies was adequately controlled, but the results are suggestive of a useful action of SK in drug-resistant epilepsy and there has been extensive experimental research on the cellular actions of this preparation [65].

Interestingly, it appears that only the crude mixture of plants which is SK possesses activity, at least in *in vitro* models [66]. Attempts to refine the preparation too far in looking for the pharmacologically active agent may prove fruitless. This is very much in line with herbalists the world over, who believe that 'the whole is more that the sum of its parts', holding that plants act synergistically within such mixtures and also that the balance of compounds within a single plant acting in concert is likely to be responsible in large part for its actions [67].

A traditional Chinese medicine (TCM) analysis is given in detail for three cases of different epilepsies by Hijikata *et al.* [68]. A Chinese traditional herbal mixture was used to very good effect as additional treatment (along with AEDs) in reducing seizure frequency in cases of epilepsy and Moyamoya disease, epilepsy with hemiparesis and hemiconvulsions and temporal lobe seizures.

In the Western world, though, the use of cannabis is probably more widespread.

In a telephone study performed from a tertiary care epilepsy centre in Canada [69], 48% of 136 patients had used marijuana at some point in their lives and 21% were active users (i.e. they had used it in the past year). There was no difference in age, sex or employment status of users versus non-users which are factors affecting use in the general population, but there were differences in the groups when considering the duration of the disease (1.6 times more likely to be marijuana users for duration < 10 years versus duration > 5 years) and seizure frequency (eight times more likely to use marijuana with 'frequent seizures'). The authors also asked participants of their knowledge of effects of marijuana in epilepsy and 56 of the 136 participants had heard of marijuana use as a treatment for epilepsy and 57% of these had heard it was beneficial. Of the active users, 12 (43%) stated 'medical reasons' (presumably related to their epilepsy) for use, though none was officially approved. It is probable that people with long-term conditions, not fully treated by conventional methods, are more likely to seek alternatives. It is, though, not impossible that frequent marijuana use leads to more severe and frequent seizures.

The use of cannabis in epilepsy might be a further example of 'synergism'. A brief report [70] tells of comparing the psychoactive ingredient of cannabis, tetrahydrocannabinol (THC), cannabis herb and a cannabis herb extract from which the THC had been removed in 'an *in vitro* model of epilepsy'. All the substances abolished 'epileptiform bursting' in the model (the details of which are, unfortunately, not specified), which suggests that not all of the therapeutic effects of cannabis are due to THC. Perhaps herbs really are more than the sum of their parts.

Dietary measures

Food sensitivity

Oligoantigenic diets and avoidance of foods to which the patient is sensitive appear to be effective in children with epilepsy and migraine, although not in those with epilepsy alone [71]. There is evidence that seizures can be precipitated in some adult subjects by eating certain foods to which they have an allergic or sensitivity response. One study used double-blinded food challenge in a 19-year-old woman with frequent seizures, a history of allergies to dust, pollen and mould, a strong family history of allergies, and an eosinophilia and who discovered by elimination diet to be sensitive to beef. Seizures occurred soon after taking capsules containing beef, but not chicken, and she remained seizure free in the long term by avoiding any beef products, having stopped anticonvulsant medication [72]. Particularly in those epileptic patients who have a strong family or personal history of allergy (asthma, allergic rhinitis or other allergy) or an eosinophilia, it is recommended to look for food sensitivities by means of exclusion diet and phased re-introduction.

Nutritional supplements

Anticonvulsant actions have been claimed in clinical trials for vitamins E and D, the trace elements selenium, manganese and zinc and the amino acid taurine. Vitamin E, in particular, has been used relatively widely [7] for its presumed anticonvulsant

activity. Thiamine and folic acid have been studied with regard to neuropathic and dental side-effects of AEDs. A Cochrane review of these studies [73] and those with vitamins E and D concluded that, in general, the number of participants is rather low and the study quality is not high. There is some evidence that thiamine can help some neuropsychological functions and vitamin D may improve bone mineral content in users of older AEDs, but folic acid does not seem to help with the neuropathy associated with some AEDs (although the number assessed in just one study was very small and the method of assessment was outdated) and only the small study (discussed below) using vitamin E demonstrated a reduction in seizure frequency, although again the numbers included were low and the confidence intervals of results wide.

This trial [74] randomized 24 subjects aged 5–18 years with various types of seizures and at least four seizures per month to receive either 294 mg (400 IU) of vitamin E ($n = 12$) or matching placebo ($n = 12$) daily for 3 months in addition to their usual AEDs. Ten of the patients in the active group were considered 'responders', that is their seizure frequency declined by at least 60%, and the two non-responders were actually non-compliant (by blood levels of vitamin E). There were no responders in the placebo group. This difference in response rate (83% versus 0%) was significant at $P < 0.05$. Blood levels of standard AEDs were not altered during the study and it was concluded that vitamin E may be a useful antiepileptic agent, at least in a paediatric population with drug-resistant epilepsy. Unfortunately, no further studies seem to have been conducted to confirm these promising preliminary results.

A single study [75] supplemented the diet of 23 adult epileptic patients with various seizure types who stayed on their standard AEDs with 4000–16 000 IU of vitamin D daily (9 patients) or placebo (14 patients). Seizure frequency declined by about 30% only whilst taking vitamin D, not on placebo, and the result was discussed in terms of the possible effects of AEDs on calcium and magnesium metabolism. The authors concluded that it might be advisable for all patients taking AEDs to receive prophylactic vitamin D. Again, this result has not been taken forward.

There is some evidence from animal studies that omega-3 fatty acids (omega-3 FAs) may increase seizure thresholds and a study has assessed their effect in refractory epilepsy [76]. This was a 12-week double-blind, placebo-controlled parallel-group study in patients with refractory epilepsy living in a residential facility. Sixty-eight patients were screened and 58 randomized. One in the group randomized to placebo was withdrawn from the trial for clinical reasons unrelated to the trial, and so 30 received active capsules containing fish oils (equivalent total daily dose 1.7 g omega-3 FAs) and 27 received matching placebo capsules containing mixed, non-fish oils. The types of epilepsy syndromes and the AEDs being used are listed and well matched in each group. A significantly greater proportion of patients taking supplements (5/30) compared with those taking placebo (0/27) had at least a 50% reduction in seizures in the first 6 weeks of the trial, but this was not sustained. There were no changes in serum AED concentrations. The authors discuss the loss of apparent efficacy after the first phase of the trial in terms of the dose of omega-3 FAs used and its purity, treatment duration, which may need to be longer, and sample size, in what some might say is not a particularly representative group of IWE in the general population.

Low levels of serum magnesium [77], manganese and zinc [78] have been reported in epileptic patients and supplementation has been reported to be sometimes helpful with seizure control.

Selenium is a widely used antioxidant supplement. Its use in epilepsy is based on findings of low selenium levels in the serum of some patients, and rare case reports suggesting potential clinical usefulness. Four children with intractable seizures since birth were found to have glutathione peroxidase deficiency, probably due to a primary deficiency in two and to defective selenium resorption or transport, as this enzyme has selenium at its active centre [79]. Supplementation with selenium and discontinuation of AEDs led to clinical improvement in all four.

The amino acid taurine has been extensively studied for its anticonvulsant properties. It appears to have only a moderate effect in general, but there are case reports of complete effectiveness in previously severe drug-resistant epilepsies [80].

Naturopathy

Naturopaths use a wide range of techniques in people with epilepsy, with the aim of allowing or stimulating the body to 'heal itself'. Any or all of the therapies discussed in this chapter can be brought to bear on the problem, but this is especially true for dietary, nutritional and homeopathic interventions [81].

Despite the wide range of evidence, there seems to be little current general enthusiasm for utilizing or researching these non-pharmacological, dietary methods of seizure control. Particularly in paediatric epilepsy, however, some of these approaches might bring worthwhile benefit.

Homeopathy

Homoeopathy is a complementary medical system which uses preparations of substances whose effects when administered to healthy subjects produce the manifestations of the disorder seen in the individual patient, so in many ways it looks for analogies between an individual patient and a substance from the natural world. It was developed by Samuel Hahnemann (1755–1843) and is now practised throughout the world [82]. This 'let like heal like' method of prescribing and the use of extremely diluted substances are the most contentious aspects of homeopathy. Large-scale meta-analyses of randomized controlled clinical trials of homeopathy [83–85], provide some evidence of activity over placebo in a wide range of conditions, even though the strength of the evidence is probably low because of the poor methodological quality of the trials. Evidence for activity of homeopathy is considered in detail elsewhere [86,87].

There are five homoeopathic hospitals within the NHS in the UK. There are no clinical trials of homoeopathy as add-on treatment in epilepsy, but there are uncontrolled case series which report improvements in seizure control [88,89]. For example, there is a case report of complete effectiveness of homeopathy in abolishing absence seizures with normalization of the EEG in a 6-year-old girl [90]. The homeopathic approach

lends itself to management of complex cases with extensive psychosocial overlay, although effectiveness in dogs may help those who feel that any effect of homeopathy must be due completely to a strong placebo response towards accepting that there is an action of remedies on the body. Ten dogs with idiopathic epilepsy (one to five tonic–clonic fits per week) were given homeopathic Belladonna 200C and no AEDs [91]. The number of fits reduced to two to three per week during the first 2 weeks after starting therapy and then no fit was reported by the owners in the next 2–8 months. Unfortunately, this is an uncontrolled study, but it helps to begin to generate ideas for future trials.

An individualized prescription is usually made, so that it is not possible to exactly list homeopathic drugs for epilepsy, as each patient will have a different prescription (of one of approximately 2500 available remedies). Experience from the Department of Developmental Neurology, Hospital for Sick Children, Glasgow, suggests that previously uncontrolled epileptic children, with seizures arising from congenital defects, birth injury, infections or other usually intractable causes, can gain improvement at the hands of a skilled homeopathic doctor [92].

Acupuncture

In its oldest form, acupuncture is a part of TCM. In traditional Chinese physiology, energy ('Qi') runs in meridians which are said to course just below the surface of the skin over the whole body. TCM encompasses an enormous range of practices including Chinese herbal medicine, Chinese acupressure and massage, dietary therapy and mind–body exercise such as Qigong and t'ai chi. It is a major established health-care system used by millions of people throughout the world for every medical condition. In TCM acupuncture, the insertion of very fine needles into the meridians at predefined points is held to re-balance blocked or excessive energy flow and so cure symptoms. It has been used for thousands of years as part of TCM treatment of epilepsy [93]. It is complex to learn this sort of approach, and Western scientists have seen the theoretical structure as off-putting.

Good results in long-term reduction of seizures [94,95] and even status epilepticus [96] have been reported, but nearly always in uncontrolled fashion or in retrospective case series. Different forms of acupuncture have been employed, but a lot of the work has been done using electro-acupuncture (i.e. stimulation of the needles by electric impulses or stimulation of the acupuncture points by surface electrodes). One study [95] reports on 98 cases of drug-resistant epilepsy treated with courses of scalp electro-acupuncture, 30 min of electrical stimulation at 2–3.5 Hz through needles placed under the scalp, given daily for 15 days and repeated with a week's break between courses. In this uncontrolled study, 89% of patients experienced a worthwhile reduction in seizure frequency and severity after a mean follow-up of 4 years.

The anticonvulsant action of acupuncture has been demonstrated in animal models and its mechanism investigated. It has been hypothesized that electroacupuncture may act as an antiepileptic via the same possible route as vagus nerve stimulation, through stimulation of the nucleus of the solitary tract [97]. Acupuncture can significantly change levels of some neurotransmitters responsible for inhibition of seizures at specific brain sites [98].

In contrast to the vast Chinese experience, many Western practitioners learn a form of acupuncture which makes fewer therapeutic claims. This 'medical acupuncture' assumes that one day it will be possible to explain all the undoubted clinical effects of acupuncture scientifically. So far, it has been most used and studied in painful conditions with good evidence of efficacy [99]. It is now a widely used therapeutic modality in, for example, physiotherapy departments and pain clinics.

It has been much more difficult to demonstrate the claimed efficacy of TCM acupuncture in systemic illness according to conventionally acceptable scientific methodology. A Cochrane review of acupuncture and epilepsy could find only three trials which met the entry criteria of acupuncture being used against a control condition, despite having no language limitation [100]. The trials were generally small and of poor quality and the review concluded that there is currently no good evidence for the effectiveness of acupuncture in epilepsy. One study, by Kloster *et al.* [101], aimed to show the effectiveness of TCM acupuncture in chronic intractable epilepsy in Norway. The authors recruited 39 patients with partial or generalized epilepsy with a duration of at least 2 years and a seizure frequency of one or more per week. Five withdrew in the 8-week baseline period. For the 8-week treatment period, they were divided into two groups by four-block randomization. One group ($n = 18$) received acupuncture and the second group ($n = 16$) acted as controls. The patients in the acupuncture group were all needled in a standard set of acupuncture points, with the possibility of one or more extra points being treated, chosen according to their TCM diagnosis. Stimulation was applied either manually or electrically (3 Hz, 3–20 mA), and all TCM diagnoses were made and the acupuncture treatments were given by two professors from the Shanghai University of TCM. The control group were given 'sham' acupuncture, that is standardized, bilateral, shallow needling of three points chosen for their minimum expected effect. Treatment time in both groups was 30 min and there were three treatment sessions per week for 7.5 weeks, with a 4-day break in the middle. Assessment of outcome was done weekly by neurologists, blind to the allocation of the subjects.

The groups were comparable in baseline characteristics, although it is a strange omission that details on use of AEDs were not reported. There was a non-significant reduction in seizure frequency in both groups, and an increase in the number of seizure-free weeks, which reached significance in the 'sham' group. There were no EEG changes of significance throughout the study and no factors could be identified which correlated with response to treatment, including age, age at onset of epilepsy, duration of epilepsy, educational level, IQ or TCM diagnosis. A subsequent paper documents the inability to detect an effect of acupuncture on health-related quality of life within this study [102]. The authors concluded that they had been unable to prove a beneficial effect of acupuncture in chronic epilepsy. The trial is certainly the study that conforms closest to the conventional norms of scientific investigation and will no doubt be taken as

convincing evidence against the use of acupuncture, but it can be criticized. The lack of information on baseline AEDs is potentially important, as the two groups could have been imbalanced by this, which is presumably at least as important a factor in 'severity' as frequency of seizures. Moreover, the study was small and the patients had a mean duration of epilepsy of 26–28 years so that the findings may not be representative for more benign epilepsies. Another important problem is the control used. The question of just what is the most appropriate control condition in acupuncture research has been much discussed. Generally, it is accepted that sham acupuncture cannot be considered a placebo, as it has measurable physiological and clinical effects [103]. If the control condition has a positive clinical effect and if the specific effect size of the active intervention is not large, then very large groups would be needed to detect a significant difference between groups. It would therefore be overhasty to conclude that acupuncture does not 'work' in epilepsy, and more research in this area is justified.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been used as a non-invasive way of evaluating, from a neurophysiological point of view, the excitatory and inhibitory functions of the cerebral cortex. It is beginning to be thought of and investigated as a possible non-pharmacological method of treating epilepsy. An excellent review of the field is provided by Tassinari *et al.* [104], but it is notable how little is said about therapeutic use in the review.

One brief report [105] describes an open pilot study in which nine patients with refractory, very frequent partial and secondary generalized seizures were treated with low-frequency, repetitive transcranial magnetic stimulation (rTMS). The subjects had experienced, on average, more than seven seizures per week in the 6 months before the study. rTMS was done on five consecutive days, using a coil placed over the vertex. Five hundred pulses at 0.33 Hz were delivered twice each study day. In the 4 weeks after the study, seizure frequency was reduced from a mean of 10.3/week in the 4 weeks prior to the study, to a mean of 5.8/week. The mean reduction in seizures per week was 36.6% (P = 0.017).

A blinded trial randomized 24 patients with localization-related uncontrolled partial and secondary generalized seizures to active or placebo rTMS stimulation at 1 Hz, delivered for 15 min twice daily for a week [106]. Stimulation was given over the scalp position best representing the ictal focus (determined by EEG). The placebo control patients underwent the same procedure, but the magnetic coil was angled 90 degrees away from the scalp. Weekly seizure frequency was compared for 8 weeks before and after 1 week of rTMS. The effect on seizure frequency was mild and short-lived in the active group compared with the placebo group. The authors try to explain this lack of apparent effect by citing the difference in stimulation frequency to the previous open trial (1 Hz versus 0.33 Hz), only giving 1 week of treatment, which may not be long enough to lead to more than a temporary reduction in seizure frequency, and the likelihood that this study may be too small to show an effect.

Further studies are needed, but rTMS may result in being a non-invasive option to add to AEDs in the control of intractable epilepsy.

Chiropractic treatment

Chiropractic therapy is a form of manipulation of the joints, particularly those of the vertebral column. As originally formulated by Daniel David Palmer, all illness stems from entrapment of spinal nerves by subluxations of the vertebrae and so all illness can be removed by manipulating these vertebral subluxations back into proper alignment. This rather rough view has been gradually replaced with a sophisticated diagnostic system and a steadily growing research base, which largely supports the use of chiropractic treatment in many areas, most (but not all) of which are related to the musculoskeletal system [107,108].

The effects of chiropractic care on the progress of epilepsy in adults remain largely unreported, but Pistolese [108] reviews 17 case reports of children with epilepsy who received chiropractic treatment. Fourteen of these were receiving AEDs that had not been successful in controlling their seizures. 'Upper cervical care to correct vertebral subluxation' was administered to 15 patients, all of whom reported positive outcomes in terms of decreased seizure activity. The critical predictor of a favourable outcome seemed to be the finding of a cervical spine malalignment in chiropractic terms. This is undoubtedly a more subtle phenomenon than most non-chiropractor clinicians are accustomed to detecting. The analysis goes no further than this and the author suggests that further investigations into the potential value of chiropractic care in paediatric epilepsy would be justified. Some of the cases detailed are truly impressive. For example, a 6-year-old girl experiencing 20–25 absence seizures per day had 'upper cervical specific adjustments to correct the atlas subluxation complex', weekly for an (unfortunately) unspecified number of weeks. There was an immediate reduction in attack frequency after the first treatment and by the end of the treatment course she was experiencing one attack per week or fewer.

Alcantara [109] reports on a 21-year-old woman who had epilepsy since childhood and now suffered a generalized tonic–clonic seizure every 3 h, lasting between 10 s and 30 min. Examination revealed very extensive abnormalities (in a chiropractic sense) in the cervical spine, and specific adjustments were administered. The seizure rate dropped to one per day by the fifth treatment session, when the treatment technique was changed. A marked increase in seizure rate followed and in fact she had a seizure during the sixth session. Rapid chiropractic adjustment at the C6–C7 level aborted the seizure immediately. Subsequent examinations showed no evidence of recurrence of the subluxation complex and all seizure activity had ceased. At 12- and 18-month follow-up, she reported minor seizures of short duration about once per month, but had experienced up to 2 months seizure free. Interestingly, in this case, the subject realized that many of her seizures were preceded by neck pain. This is the only report of successful acute treatment of an epileptic seizure by chiropractic manipulation. The authors discuss models of how upper spine malalignment might lower seizure threshold, invoking concepts of seizure triggering by sensory input to the brain

and aberrant sensory impulses from a disordered cervical spine. Again, they call for more research.

These case reports are well written and document apparent beneficial effects of chiropractic care in some patients with epilepsy at least as clearly as many case reports for the psychological treatments mentioned earlier. There are a number of controlled studies demonstrating specific effects of chiropractic care in different clinical conditions against a variety of inventive placebo conditions [110]. Controlled trials may be justified in those patients with epilepsy who have cervical spine disorders demonstrable by chiropractic techniques.

Conclusions

Most of the studies and case reports discussed in this chapter are based on uncontrolled observations, and therefore claims of therapeutic success should be interpreted with caution. In randomized trials, many patients with epilepsy may respond well to placebo, which may be explained by emotional influences on seizure activity and also by the phenomenon of the regression to the mean (i.e. the tendency of patients to seek medical attention during periods of seizure exacerbation, which tend to be naturally followed by a spontaneous decline of seizure frequency towards its average value). While these limitations should be kept in mind, the evidence discussed in this chapter does suggest that some of the non-pharmacological approaches reviewed above may have worthwhile efficacy, and high-quality research should be supported in the more suggestive areas. In particular, there appears to have been a peculiar blindness to the benefits which can be obtained from behavioural techniques such as EEG biofeedback and dietary measures such as oligo-antigenic diets. The patients are already using many of these treatments, sometimes without divulging this fact to their medical attendants, with all that implies. An effective way to select patients and advise them about particular treatments should be the aim.

Love it or loathe it, patients with epilepsy will continue along their pragmatic therapeutic paths. It would be of benefit to all if their caregivers could, if not walk with them, guide them safely.

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25 Reproductive Aspects of Epilepsy Treatment

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While reproductive health is regarded as one of the most important health issues for women with epilepsy, surveys in different countries have repeatedly revealed marked deficiencies in the provision of health care and advice on this issue. Only a minority of women with epilepsy who plan to have children have any pre-pregnancy counselling and knowledge among health-care providers about the reproductive health of women with epilepsy is often inadequate. To be worthwhile, counselling should ideally be provided long before pregnancy in order to allow for adequate treatment measures which reduce risks. Reproduction may be more complicated for people with epilepsy for a number of reasons related to epilepsy and to its treatment. Although most women with epilepsy will be able to give birth to perfectly normal children, a number of questions are raised when they consider becoming pregnant, and these need to be addressed early in the pregnancy planning.

Fertility may be altered, and the efficacy of steroid oral contraceptives may be reduced by certain antiepileptic drugs (AEDs). Epilepsy might affect the outcome of pregnancy and there may be increased risks of obstetric complications. Seizure control may change during pregnancy and treatment may need to be adjusted because of altered pharmacokinetics of AEDs. Fetal risks associated with uncontrolled seizures during pregnancy need to be weighed against the teratogenic effects and other potential developmental toxicity of AEDs. The possibility for a woman on AEDs to nurse her child also needs to be discussed.

Fertility

Studies indicate lower fertility rates among men and women with epilepsy than in the general population [1]. There are many possible causes for reduced fertility rates among people with epilepsy. Social isolation and stigmatization may contribute, which also explain why marriage rates are reported to be lower. Women may also refrain from pregnancy because of fears of deterioration in their epilepsy or risks to the fetus incurred by seizures or the drug treatment. The lesion causing epilepsy and the epileptic activity as such may also induce endocrine dysfunction that could affect fertility. Some studies, however, suggest that concurrent disabilities and co-morbidities (e.g. learning disabilities or cerebral palsy) could be the major cause [2,3]. Fertility rates among people with epilepsy were essentially normal in two population-based studies from Iceland and Finland when people with such severe co-morbidities were excluded [2,3]. Treatment with AEDs has also been considered to contribute to lower fertility and other reproductive dysfunction.

Reproductive dysfunction

Reproductive dysfunction and endocrine disorders are common among both men and women with epilepsy. In men, this will manifest itself as loss of libido, reduced potency and infertility; in women, by menstrual dysfunction, hirsutism and infertility. In some studies, between 40% and 70% of men with epilepsy report decreased potency and hyposexuality, but this apparently high figure needs to be related to the proportion among control populations [4]. Rättyä *et al.* [5] evaluated sexual function, including libido, potency, satisfaction with erection and orgasm, in men, 18–50 years of age, under treatment with an AED in monotherapy. Of these, 77% were considered to have a normal sexual function compared with 88% among healthy age-matched control subjects. Menstrual disorders are more common among women with epilepsy, occurring in one-third compared with 12–14% in the general population [6].

Whether reproductive dysfunction is related to the underlying epilepsy is still controversial, but it has been suggested that epileptiform discharges may promote the development of reproductive endocrine disorders by disruption of normal temporo-limbic modulation of hypothalamopituitary function [6]. This hypothesis is supported by observations of lower testosterone levels in men with temporal as compared with extratemporal foci and that successful temporal lobe epilepsy surgery may lead to a normalization of low preoperative serum androgen concentrations [7].

Treatment with AEDs can also contribute to reproductive dysfunction. Enzyme-inducing drugs such as carbamazepine, phenytoin and phenobarbital may increase the concentration of sex hormone-binding globulin (SHBG) and reduce the unbound, biologically active concentrations of testosterone [8]. In a cross-sectional study, monotherapy with carbamazepine was associated with decreased serum androgen levels and high SHBG concentrations in men with predominantly partial seizures. Oxcarbazepine treatment in doses of at least 900 mg/day was associated with similar endocrine effects. In contrast, serum androgen levels were increased in 12 out of 21 men treated with valproic acid for generalized or partial seizures [5].

Infertility in men may also be related to impaired spermatogenesis or sperm function. Poor sperm motility was noted in epileptic patients with long-term AED treatment and *in vitro* studies

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suggest a direct effect of phenytoin, carbamazepine and valproic acid on sperm membrane function [9]. A cross-sectional small study of men with epilepsy suggested that all investigated drugs, carbamazepine, oxcarbazepine and valproic acid, were associated with an increase in abnormal sperm morphology [9], although the clinical relevance of these findings remains to be shown.

The discussion on reproductive endocrine disorders in women with epilepsy has focused on polycystic ovaries (PCO) and polycystic ovarian syndrome (PCOS). PCO, which is normally a diagnosis made on ultrasound examination and which may be asymptomatic, is a common condition with an estimated prevalence of about 20% in the general population. PCOS has been defined as ovulatory dysfunction with clinical evidence of hyperandrogenism and/or hyperandrogenaemia in the absence of identifiable adrenal or pituitary pathology, although criteria vary between researchers. PCOS is a syndrome with multiple aetiologies and a prevalence ranging from about 4% up to 18% in the general female population, depending on the criteria and the population studied and probably higher, 10–20%, in women with epilepsy [6]. Genetic as well as environmental factors can contribute to the development of this syndrome.

Cross-sectional studies from Finland, Norway, the Netherlands and the UK have indicated that polycystic ovaries and hyperandrogenism, and PCOS are related to the drug treatment and specifically to treatment with valproic acid [8]. In these studies 30–40% of patients treated with valproic acid had polycystic ovaries and hyperandrogenism, compared with 5–15% among those taking carbamazepine or lamotrigine. However, two studies from other epilepsy populations found no difference between women taking valproic acid and carbamazepine in this respect [10,11]. A randomized open-label study compared the development of PCOS after 12 months on valproic acid and lamotrigine [12]. Hyperandrogenism and ovulatory dysfunction was found in 44% of those randomized to valproic acid compared with 23% of those on lamotrigine if treatment was initiated before 26 years of age, whereas the rates were similar (24% versus 22%) if treatment was started above 26 years.

In many patients, reproductive endocrine dysfunction appears to be reversible on withdrawal of or change in AED treatment. A switch from valproic acid to lamotrigine in women with polycystic ovaries and hyperandrogenism whilst on valproic acid was associated with normalization [8], and so was withdrawal of valproic acid in a large proportion of patients in a 5-year follow-up study [13]. Taken together, these observations confirm that valproic acid can indeed induce polycystic ovaries and hyperandrogenism, although the role may not be as important as reported in the initial cross-sectional studies from Finland.

Withdrawal of carbamazepine in seizure-free male and female patients has also been associated with normalization (increase) of serum testosterone and free androgen index [14].

Two cross-sectional studies assessed endocrine function in a younger female population with epilepsy [15,16]. A cohort of 77 girls, 8–18 years of age, under treatment with valproic acid (n = 40), carbamazepine (n = 19) or oxcarbazepine (n = 18) were compared with 49 healthy age-matched controls. No difference was observed in linear growth and sexual maturation [15]. When 41 girls on valproic acid were compared with 54 healthy controls, hyperandrogenism was observed more frequently among the valproic acid-exposed girls, but the incidence of polycystic ovaries or menstrual disturbances was not increased [16]. A long-term follow-up of these cohorts revealed normal endocrine function in those that had come off medication but an increased prevalence of endocrine disorders including PCOS among those remaining on AEDs into adulthood [13].

Choice of antiepileptic drug

Given the partly conflicting data concerning the association between valproic acid and reproductive dysfunction, and the excellent effectiveness of this drug, particularly in idiopathic generalized epilepsies, valproic acid is still a reasonable first choice in young women with these types of epilepsy, unless they can be assumed to become pregnant while on treatment (see below). However, based on the intriguing observations discussed above, the patients should be monitored closely. If adverse effects such as considerable weight gain or menstrual disturbances occur, a change in drug therapy should be considered. The potential role of AEDs always needs to be considered in women and men with epilepsy with reproductive dysfunction, and in such cases it may be necessary to reassess the choice of treatment [17].

Birth control

Contraception in women with epilepsy is complicated by the bidirectional pharmacokinetic interactions between AEDs and steroid oral contraceptives. Enzyme-inducing AEDs may reduce the effectiveness of oral contraceptives by inducing the metabolism of the oestrogen and progestagen components, and possibly also by increasing the hepatic synthesis of SHBG, thus decreasing the unbound, active concentration of progestagen. This may lead to contraceptive failure and an increased frequency of unplanned pregnancies [18]. AEDs with and without known inducing effects on oral contraceptives are listed in Table 25.1.

Depot injections of medroxyprogesterone, hormone-releasing intrauterine systems and other intrauterine contraceptive devices seem to be unaffected by enzyme inducers and could be good alternatives for some women [18].

If this is not an alternative, patients treated with enzyme-inducing AEDs are often recommended oral contraceptives with an oestrogen content of at least 50 μg. Whether this dose is sufficient, however, is uncertain. Others, therefore, recommend either the use of a combined oral contraceptive with a progestin dose well above the dose needed to inhibit ovulation, or continuous use of combined contraceptive pills without a pill-free interval [19]. Where available, tricycling is another alternative. These are combined oral contraceptives given continuously for three sets of 21 days followed by 7 days' pause.

Estradiol-containing oral contraceptives, on the other hand, induce the elimination of lamotrigine. Lamotrigine serum concentrations decline by approximately 50% when such contraceptives are introduced. This can lead to breakthrough seizures unless the lamotrigine dose is adjusted. These changes occur rapidly and hence lamotrigine levels rise during the pill-free week if sequential pills are used [20]. This may induce toxic symptoms. Preliminary data suggest that estradiol may have a similar effect on serum concentrations of valproic acid. Pure progestagen-containing pills

Table 25.1 Pharmacokinetic interactions between steroid oral contraceptives and antiepileptic drugs.

Drugs which increase the clearance of oral contraceptives	Drugs which do not affect the clearance of oral contraceptives	Drugs in which the clearance is induced by estradiol-containing oral contraceptives
Carbamazepine	Benzodiazepines	Lamotrigine
Felbamate	Gabapentin	Valproic acid
Lamotrigine[a]	Levetiracetam	
Oxcarbazepine	Pregabalin	
Phenobarbital	Tiagabine	
Phenytoin	Valproic acid	
Topiramate (at dosages >200 mg/day)	Vigabatrin	
	Zonisamide	

[a] Lamotrigine does not affect estradiol concentrations but has a modest effect (18% reduction in plasma concentration) on the norgestrel component of the combined oral contraceptive.

do not seem to affect lamotrigine serum concentrations, and concomitant use of valproic acid appears to block the estradiol-induced effects on lamotrigine kinetics [21].

Women need to be informed about these clinically relevant bidirectional interactions. Enzyme-inducing properties should be taken into account when choosing an AED for a woman on oral contraceptives. Given the choice of two drugs similar in all other important respects it is reasonable to select a drug known not to interact with oral contraceptives. The possibility of using complementary or alternative contraceptive methods should also be discussed, and it should be stressed that the effectiveness of many contraceptive methods other than the intrauterine device may actually be lower than that of an oral contraceptive taken together with enzyme-inducing drugs. Women on lamotrigine who are started on estradiol-containing pills should have their dosage increased guided by drug level monitoring, and pills are best avoided.

Pregnancy in women with epilepsy

In the treatment of epilepsy during pregnancy, maternal and fetal risks associated with uncontrolled seizures need to be weighed against the increased risk of adverse outcomes in the offspring due to maternal use of AEDs.

Effects of maternal seizures on the fetus

Epileptic seizures in a pregnant woman may have adverse effects on the fetus, in addition to risks for the woman. With respect to the risks to the fetus, effects of generalized tonic–clonic seizures are probably different from effects of other types of seizures [22]. Tonic–clonic seizures are associated with transient lactic acidosis, which is likely to be transferred to the fetus. Prolonged decrease in fetal heart rate, which is a common response to acidosis, has been reported after maternal tonic–clonic seizures. Furthermore, generalized tonic–clonic seizures induce alterations in blood pressure and blood flow, but it is presently not known to what extent this affects uterine blood flow and thus the fetus. Seizure-related maternal abdominal trauma could also, theoretically, cause injury to the fetus or placental abruption. Despite these effects, intrauterine fetal death as a result of a single seizure appears to be rare and only a few such reports have been published. In contrast, prolonged seizure activity, such as status epilepticus, may be a serious threat to the fetus as well as to the woman. In an early review, fetal death was reported in about 50% of cases with status epilepticus during pregnancy, and in 30% of the mothers [23]. This is in contrast to the results of a recent large prospective study, which reported only one case of intrauterine death and no maternal mortality among 36 women with status epilepticus (12 of whom were convulsive) [24]. According to most prospective studies, seizures during early pregnancy are not associated with an increased risk of birth defects. However, occasional reports have indicated an increased risk for cognitive dysfunction in the offspring of women who have had more than five convulsive seizures during pregnancy [25], although conclusive evidence for a causative role of the seizures is lacking.

Other types of seizures are in general unlikely to affect the fetus when they occur during pregnancy unless they lead to a secondarily generalized tonic–clonic seizure. However, they may cause some risks if the seizure results in injury or trauma.

Generalized tonic–clonic seizures during labour can cause fetal asphyxia. Partial seizures that impair consciousness may also impose risks since the mother's ability to co-operate during the delivery is lost. In such situations, Caesarean delivery should be considered.

In conclusion, our knowledge concerning fetal risks associated with maternal seizures is based on case reports rather than systematic studies and we lack quantitative risk estimates. Nevertheless, there is a general consensus among physicians that in particular generalized tonic–clonic seizures should be avoided during pregnancy for the sake of the well-being of the fetus as well as the mother.

Seizure control during pregnancy and delivery

The largest prospective study of seizure control in pregnancy to date reported that 59% of 1736 women remained seizure free throughout pregnancy [24]. Earlier studies, mainly from specialized epilepsy centres, indicated that approximately one-third of women with epilepsy will experience an increase in seizures during pregnancy [26]. Prospective studies of fewer selected women with epilepsy suggest that the proportion of women who deteriorate is smaller [22]. Some of the observed changes in seizure frequency are likely to be explained by the normal spontaneous fluctuations in seizure occurrence, but it appears that some periods of pregnancy are associated with a significant increase in seizures. A generalized tonic–clonic seizure occurs during labour in about 1–2% and within 24 h after delivery in another 1–2% [22]. Taking all seizure types together, roughly 5% of women with epilepsy will experience seizures during labour, delivery or immediately thereafter.

Status epilepticus occurs in less than 1% of all pregnancies of women with epilepsy and does not seem to occur more frequently during pregnancy than in other periods of life.

Most studies report that patients with a satisfactory seizure control before pregnancy are less likely to deteriorate than patients with uncontrolled epilepsy [27]. There are observations

suggesting that those women who fail to have prepregnancy counselling are most at risk of deterioration during pregnancy. This agrees with several reports indicating that poor compliance with the drug treatment, often due to fear of the teratogenic effects, is a major cause of loss of seizure control during pregnancy.

Some women may experience onset of a seizure disorder during pregnancy, and they should be investigated according to the same general principles as non-pregnant patients with new-onset epilepsy, although there are some causes of seizures that need to be considered more specifically. If seizures occur for the first time during the last 20 weeks of pregnancy, eclampsia needs to be excluded. Stroke and cerebral venous thrombosis also occur at a higher frequency during pregnancy. The general principles for initiation and choice of AED treatment also apply for women in pregnancy, although treatment is often withheld during the first trimester unless the risk is high for recurrent tonic–clonic seizures.

Pharmacokinetics of antiepileptic drugs during pregnancy

The pharmacokinetics of many drugs undergoes significant changes during pregnancy, which may have consequences for maternal seizure control as well as for fetal drug exposure [28]. At constant drug dosages, serum levels of most of the older AEDs tend to decrease during pregnancy, and return to prepregnant levels within the first month or two after delivery. This appears to be due mainly to a decrease in drug binding to plasma proteins and/or an increase in drug metabolism and elimination. A decrease in protein binding will result in lower total drug levels but leave unchanged the unbound, active concentration of the drug.

By the end of pregnancy, total and unbound concentrations of phenobarbital decline by up to 50% [28]. Total concentrations of carbamazepine decline to a lesser extent and the changes in unbound concentrations are insignificant [28]. Marked decreases in total phenytoin concentrations to about 40% of prepregnancy levels have been reported [28], whereas free concentration decreased to a much lesser extent. For valproic acid, no significant changes were noted in unbound concentrations despite a fairly marked decrease in total concentrations [28]. Hence, for highly protein-bound drugs such as valproic acid and phenytoin, total plasma concentrations may be misleading during pregnancy, underestimating the pharmacological effects of the drugs.

The most pronounced changes have been reported with lamotrigine. In some patients, serum concentrations may decline in late pregnancy to 30% of prepregnancy levels with normalization within a few days post partum [28]. Such alterations in serum concentrations have frequently been associated with deterioration in seizure control [29]. Preliminary data suggest a similar decline in serum concentrations of the active moiety of oxcarbazepine [28] and a fall in serum concentrations of levetiracetam of up to 50% has also been reported [30].

The figures quoted above represent average changes for groups of patients, while the effect of pregnancy varies between individuals. The decline in plasma concentration may be insignificant in some patients and pronounced in others, prompting dosage adjustments to maintain seizure control. Monitoring drug levels is therefore recommended during pregnancy. For highly protein-bound AEDs such as valproic acid and phenytoin, unbound drug levels should ideally be measured. A single drug level is of limited value since the optimal concentration is individual. When pregnancy is planned in advance, it is therefore advisable to obtain serum drug concentrations before pregnancy, when seizure control is optimal, in order to establish a baseline to be used for comparison purposes.

Obstetric complications during pregnancy and delivery

The literature on rates of obstetric complications in pregnant women with epilepsy is somewhat conflicting. Earlier studies suggest that induction of labour and instrumental deliveries are more frequent in women with epilepsy. This may be a consequence of fear of seizures and unfamiliarity with epilepsy among obstetricians rather than a reflection of an increased rate of obstetric complications. More recent studies suggest that, with modern management, there is no significant increase in common obstetric complications among women with well-controlled epilepsy [22,31,32]. However, a Caesarean section might be needed if frequent seizures greatly impair co-operation in the forthcoming labour and delivery or if a generalized tonic–clonic seizure occurs during labour [22]. For these reasons, pregnant women with epilepsy should be counselled by obstetricians who are familiar with epilepsy-related problems and delivery should take place in well-equipped obstetric units.

Developmental toxicity of antiepileptic drugs

The first reports of adverse effects of AEDs on the fetus were published in the 1960s. Since then, all of the major old-generation AEDs, such as phenobarbital, phenytoin, valproic acid and carbamazepine, have been shown to be teratogenic. Adverse effects reported in exposed infants include major congenital malformations, minor anomalies and dysmorphism, growth retardation and impaired postnatal cognitive development. Although the pathogenesis is likely to be multifactorial, including genetic predisposition, socioeconomic circumstances, seizures and epilepsy, the available data strongly suggest that AEDs are the major cause of the increased risks.

Major congenital malformations

A large number of retrospective and prospective cohort studies have confirmed an increased frequency of major malformations in offspring of women treated with AEDs. The prevalence of major congenital malformations has ranged from 4% to 10%, corresponding to a two- to fourfold increase compared with the expected [22,33,34]. Differences in treatment strategy, study populations, controls and criteria for malformations can account for the variation in outcome [34]. Some studies have included untreated women with epilepsy as additional controls. In general, such studies have not found an increased malformation rate among children of mothers with untreated epilepsy [35], suggesting that the increased risk for major malformations in the offspring of women taking AEDs is due to the drug therapy rather than the epilepsy.

Although all major older generation AEDs have been shown to be teratogenic, it is not until recently that sufficiently large studies have been carried out to compare different AEDs with respect to their teratogenic potential. The prevalence of major malforma-

Table 25.2 Malformation rates (%) in infants exposed *in utero* to antiepileptic drugs in monotherapy recently reported from pregnancy registries (*n* = offspring with malformations).

Study	Carbamazepine			Lamotrigine			Phenobarbital			Phenytoin			Valproic acid		
	Total outcomes	*n*	%	Total outcomes	*n*	%	Total outcomes	*n*	%	Total outcomes	*n*	%	Total outcomes	*n*	%
Swedish Medical Birth Registry [36]	703	28	4.0	90	4	4.4				103	7	6.8	268	26	9.7
Finnish Drug Prescription Registry [37]	805	22	2.7							38	1	2.6	263	28	10.6
UK Epilepsy and Pregnancy Register [38]	927	20	2.2	684	21	3.1				85	3	3.5	762	44	5.8
GSK International Lamotrigine Registry [39]				802	22	2.7									
Australian Epilepsy and Pregnancy Register [27]	234	7	3.0	146	2	1.4				17	1	5.9	166	22	13.3
North American Epilepsy and Pregnancy Registry [40]							77	5	6.5						
North American Epilepsy and Pregnancy Registry [42]				564	15	2.7									
North American Epilepsy and Pregnancy Registry [43]	873	23	2.6												
North American Epilepsy and Pregnancy Registry [41]													149	16	10.7

tions in some recent large studies are summarized for the most frequently used drugs in Table 25.2 [36–43]. Malformation rates in association with exposure to a specific AED as monotherapy vary between studies, which could be explained by differences in methodology. However, the prevalence of malformations among children exposed to carbamazepine is consistently fairly low (2.2–4.0%). This observation indicates that with monotherapy and modern management the risks might not be as greatly increased as previously thought. Second, it appears that malformation rates are higher in association with valproic acid than with carbamazepine, and that the risk of major malformations with lamotrigine is similar to that of carbamazepine. Unfortunately, the numbers of pregnant women on other newer generation drugs are still too small to allow a meaningful analysis. Even within-study comparisons of malformation rates need to be interpreted with caution considering the possible effects of confounding factors in these observational studies. Even larger studies are needed to analyse the contribution of seizure control, type of epilepsy, family history of birth defects, and so on.

The drug dosage also needs to be considered in any comparison. A dose–effect relationship has been demonstrated for valproic acid, with significantly higher risks for birth defects with doses exceeding 800–1000 mg/day [22,27,33,37]. One recent study also reported a positive dose–response for malformations with lamotrigine exposure. Doses above 200 mg/day were associated with higher risks [38]. This, however, was not confirmed in the manufacturer's own lamotrigine pregnancy registry [39]. Polytherapy has consistently been associated with a higher risk for major congenital malformations than monotherapy [22,33].

Pregnancy registries have generally compared overall malformation rates, but the pattern of birth defects differs between drugs [22]. Orofacial clefts, congenital heart defects and distal digital defects are more common in children exposed to phenytoin and barbiturates. Valproic acid exposure has been associated with an increased risk of neural tube defects, reported to occur in 1–2% of exposed infants. Valproic acid has also been associated with skeletal abnormalities including radial aplasia. A risk of neural tube defects of 0.5–1% has also been reported after carbamazepine exposure. Carbamazepine is also associated with an increased risk of congenital heart defects and, recently, lamotrigine was reported to be associated with a significant increase in the risk of oral clefts [42].

Minor anomalies and fetal antiepileptic drug syndromes

Minor anomalies are structural variations that are visible at birth but without medical, surgical or cosmetic importance. Such anomalies are common in normal unexposed infants but have been reported to occur more frequently in infants of mothers treated for epilepsy during pregnancy. Combinations of several anomalies are less frequent and can form a pattern, or a dysmorphic syndrome, which may indicate a more severe underlying dysfunction. Facial features such as hypertelorism, depressed nasal bridge, low-set ears, micrognathia and distal digital hypoplasia, sometimes in combination with growth retardation and developmental delay, were first reported in association with exposure to phenytoin. Subsequently, however, similar patterns have been associated with exposure to carbamazepine. Valproic acid exposure has been claimed to cause a somewhat different dysmorphic syndrome characterized by thin arched eyebrows, broad

nasal ridge, short anteverted nose and thin upper lip [44]. However, there is a considerable overlap in the various dysmorphisms and their drug specificity has been questioned [45]. A more general term of fetal or prenatal AED syndrome has therefore been suggested. In addition, the pathogenesis is still somewhat controversial, and Gaily *et al.* [46] attributed most of the minor anomalies to genetic factors rather than drug exposure. Finally, it should be emphasized that minor anomalies are much more difficult to assess objectively than major malformations, and that the incidence of minor anomalies in exposed infants varies markedly between studies.

Growth retardation

Reduced birth weight, body length and head circumference in the offspring of women treated with phenytoin was reported as early as the 1970s. Reductions in body dimensions, in particular head circumference, have been confirmed in several subsequent studies of larger cohorts [47,48]. Most studies report a more pronounced effect in infants exposed to polytherapy. However, the association with specific AEDs in monotherapy varies. Some investigators found an association with phenobarbital and primidone, whereas others report carbamazepine to be more strongly associated with a small head circumference. In a more recent publication, Wide *et al.* [49] studied body dimensions in infants exposed to AEDs *in utero* in a Swedish population over a period of 25 years comparing data with those of the general population. There was a clear trend towards normalization of the head circumference over the time period in parallel with a shift from polytherapy towards monotherapy despite an increasing use of carbamazepine.

Postnatal cognitive development

One of the most important issues is whether exposure to AEDs *in utero* could adversely affect postnatal cognitive development. Long-term follow-up studies of large cohorts of exposed individuals are necessary in order to address this issue. Such studies are difficult to perform and also complicated to interpret since environmental factors become more important with increasing age of the child. A Cochrane review concluded that the majority of earlier studies are of limited quality and that there is little evidence about which drugs carry more risks than others to the development of children exposed [50]. A few studies have been published since then, and indicate that exposure to valproic acid might be associated with specific adverse cognitive effects [25,51,52]. A retrospective study from the UK found significantly lower verbal intelligence quotient (IQ) in 41 children exposed to valproic acid than in unexposed and in children exposed to carbamazepine ($n = 52$) or phenytoin ($n = 21$) [25]. Multiple regression analysis identified exposure to valproic acid, five or more tonic–clonic seizures in pregnancy and low maternal IQ to be associated with lower verbal IQ also after adjustment for confounding factors. Doses above 800 mg/day were associated with lower verbal IQ than were lower doses. These important signals need to be confirmed or refuted in prospective studies. Two small prospective population-based studies from Finland found similar trends for lower verbal IQ in children exposed *in utero* to valproic acid, although the studies were too small (13 children exposed to valproic acid monotherapy in each) to demonstrate statistically significant associations [51,52].

Hence, adequately powered prospective studies are urgently needed to assess long-term cognitive effects of exposure to valproic acid and other AEDs.

Sensitive periods

Sensitive periods in embryonic development with reference to some of the more important major malformations associated with AEDs are summarized in Table 25.3. Obviously, adverse effects of this type occur early, often before the woman is aware that she is pregnant. In contrast, drugs may affect growth and cognitive development throughout pregnancy.

Breastfeeding

Most drugs pass from maternal plasma to breast milk and are transferred to the nursed infant. In general, the amounts thus transferred are much smaller than those transferred via the placenta during pregnancy. The amount that the infant will be exposed to through breastfeeding depends on the maternal plasma concentration, the extent of transfer to breast milk and the amount of milk intake by the infant. Drug exposure of the suckling infant is also dependent on the infant's absorption, distribution, metabolism and elimination of the drug. In particular, metabolism and excretion may be markedly different in the infant compared with children and adults and also vary with the drug in question. Relevant pharmacokinetic information is summarized in Table 25.4 [30,53,54].

Table 25.3 Gestation periods sensitive to specific congenital malformations.

Malformation	Approximate sensitive period (gestational weeks)
Neural tube defects	3–4
Congenital heart defects	4–8
Orofacial clefts	6–10

Table 25.4 Antiepileptic drugs in breast milk and in the breast-fed infant.

Antiepileptic drug	Milk–maternal plasma concentration ratio	Infant–maternal plasma concentration (%)
Carbamazepine	0.1–0.3	10–20
Clobazam	0.1–0.4	
Ethosuximide	0.8–1.0	40–60
Felbamate	?	
Gabapentin	0.7–1.3	4–12
Lamotrigine	0.4–0.8	25–50
Levetiracetam	0.8–1.3	<20
Oxcarbazepine[a]	0.5–0.8	7–12%
Phenobarbital	0.3–0.5	50–100
Phenytoin	0.1–0.6	<10
Pregabalin	?	
Tiagabine	?	
Topiramate	0.7–1.1	9–17
Valproic acid	0–01–0.1	<5
Zonisamide	0.9	

[a] Refers to the active mono-hydroxy metabolite of oxcarbazepine.

For carbamazepine, gabapentin, levetiracetam, oxcarbazepine, topiramate and valproic acid, only small amounts are transferred and serum levels in suckling infants are generally so low that pharmacological effects are unlikely to occur. For ethosuximide and lamotrigine, infant serum concentrations may occasionally reach levels at which pharmacological effects can be seen. However, so far there is no clear evidence for the occurrence of adverse effects in nursed infants. Phenobarbital, and phenobarbital as a metabolite of primidone, can accumulate in the suckling infant, and sedation and poor suckling have been reported. Similarly, sedation may occur due to exposure to benzodiazepines such as diazepam, clonazepam and possibly clobazam if taken chronically by the nursing mother. However, such adverse effects do not occur in all nursed infants.

The benefits of breastfeeding in general are unquestionable. These must be weighed against the possible risks to the infant induced by drug exposure. Taking this into account, women with epilepsy should, in general, be encouraged to nurse their infants, and the risk for adverse effects due to drug exposure through breast milk is, in most cases, negligible.

Women who nurse while taking phenobarbital, primidone, benzodiazepines and perhaps also ethosuximide and lamotrigine should be encouraged to monitor their infant for side-effects such as sedation or poor suckling, rather than being advised not to nurse. If suspicion of pharmacological effects arises, this could be confirmed or rejected by measuring serum drug levels in the infant.

Folate supplementation

Low folate intake has been associated with an increased risk of congenital malformations, in particular neural tube defects, in animal studies and in humans. In a randomized study of more than 7000 Hungarian women planning pregnancy, supplementation with 0.8 mg folic acid reduced the risk of neural tube defects significantly [55], demonstrating the effectiveness of folate for prevention of first occurrence of neural tube defects. A randomized British study [56] assessed the effect of folic acid supplementation on the risk of recurrence of neural tube defects in high-risk pregnancies. More than 1000 pregnancies were included and 4.0 mg/day folate reduced the recurrence risk by 72%. Periconceptional intake of 0.4 mg of folic acid daily has also been shown to reduce the risk of neural tube defects in a public health campaign in China [57]. Unfortunately, no randomized study has specifically assessed the effectiveness of folic acid supplementation in women with epilepsy. In fact, such patients were excluded from the study in the UK [56].

In the absence of data specific for women with epilepsy, recommendations have to be drawn from studies based on the general population. In general, women of child-bearing potential are recommended a daily intake of 0.4 mg folic acid, and the most practical way of achieving that is as a daily supplementation. It is reasonable to suggest this also to all women with epilepsy. A higher dose of 4 mg/day is recommended for secondary prevention to women with a previous history of giving birth to a child with neural tube defects or with a family history of such malformations. However, as AED use is associated with an increased risk of neural tube defects and other malformations, many guidelines recommend that all women under treatment with such drugs should take up to 5 mg of folate per day from before conception and throughout the first trimester [22,58]. However, it is essential to inform the patient that it is uncertain whether folate supplementation will reduce this risk induced by AEDs [59], and pregnancy monitoring with prenatal diagnosis should be offered in the same way whether or not high-dose folate is prescribed.

Vitamin K supplementation and neonatal haemorrhage

Vitamin K deficiency can cause early neonatal haemorrhage, and neonates of mothers treated with enzyme-inducing AEDs during pregnancy may have an increased risk. Decreased levels of vitamin K-dependent clotting factors are found in the cord blood of newborns of women taking enzyme-inducing AEDs, and supplementation with 10 mg/day of vitamin K orally for the last month of pregnancy has been shown to normalize these levels. It remains to be shown that prenatal oral vitamin K supplementation also reduces the risk of neonatal haemorrhage. Hey [60] studied prospectively cord blood prothrombin time in 137 babies born to women on phenobarbital, phenytoin or carbamazepine. Only 14 of the babies had prolonged prothrombin time and none an overt bleeding tendency. The abnormality was corrected within 2 h by 1 mg of parenteral vitamin K. Based on these observations, Hey concluded that evidence is lacking for a particular early form of neonatal haemorrhage related to use of anticonvulsants, and that oral vitamin K supplementation during late pregnancy is unjustified, where intramuscular injections of vitamin K to the newborn are routine. This notion is further supported by two more recent controlled studies that failed to find an increased risk of neonatal haemorrhage related to the use of enzyme-inducing AEDs [61,62].

Preconception counselling

Several surveys have revealed that women with epilepsy often receive insufficient and even inaccurate information concerning issues related to reproductive function. Clinical practical guidelines for the care of women with epilepsy of child-bearing age have been published in many countries [58]. Unfortunately, many important questions are still unanswered, and many of the recommendations build on rather weak evidence, from observational studies rather than randomized trials. This is reflected in the slight differences found in the different guidelines. Nevertheless, they provide useful tools and need to be brought to the attention of health-care providers and utilized in their counselling of women with epilepsy. An optimal management of pregnancy depends largely on considerations that have to be made, and measures that have to be taken, before conception. Prepregnancy counselling is therefore essential, and it is an important challenge to change the present situation whereby such counselling seems to be offered to only a minority of women with epilepsy. Preconceptional counselling should cover the issues listed below.

- Contraception and fertility. The bidirectional interaction between hormonal contraceptives and AEDs should be discussed when relevant. The possibility that drug treatment may induce endocrine dysfunction affecting fertility should also be addressed.

- Genetic counselling with respect to the risk of giving birth to a child who will develop epilepsy and with respect to birth defects.
- Risks associated with seizures during pregnancy, and information that such risks to the fetus probably outweigh the risks incurred by an optimized treatment with AEDs.
- Risks of adverse effects of AEDs to the fetus, including a two- to fourfold increase in the incidence of major malformations.
- The option of prenatal diagnosis of birth defects, including possibilities and risks with the different methods.
- General principles of AED use in pregnancy, and the importance of optimizing seizure control and making any major change in drug therapy before pregnancy. The importance of medication compliance during pregnancy and the risks associated with abrupt withdrawal need to be underlined.
- Recommendations concerning folate supplementation, including information on the lack of evidence for its effectiveness in preventing birth defects related to AED exposure.
- Risk of seizures at delivery and the recommendation that delivery should take place in well-equipped obstetric units.
- Risk for deterioration in seizure control due to sleep deprivation after delivery.
- Feasibility of breastfeeding.

In conclusion, although there are specific risks and problems associated with pregnancy in women with epilepsy, counselling should focus on the feasibility of reducing risks and on the fact that more than 90% of women with epilepsy can look forward to an uneventful pregnancy and to giving birth to a normal and healthy child.

Some of the issues discussed above (e.g. genetic counselling and the risk for deterioration in seizure control due to sleep deprivation) are also relevant for men with epilepsy who are considering having children, although this is often completely neglected.

Table 25.5 Optimizing treatment of epilepsy in pregnancy.

Women seeking advice before *becoming pregnant*
All attempts at major changes in drug treatment should be accomplished and adequately assessed before conception
Confirm diagnosis of active epilepsy and reassess need for treatment with antiepileptic drugs
For women in remission, gradual withdrawal of antiepileptic drugs may be considered if the risk of recurrence is low and the woman is aware of the risks and potential consequences
For women who need treatment, select the appropriate drug for the patient's seizures or epilepsy syndrome but avoid valproic acid if possible
Aim at monotherapy and try out the lowest effective dosage of the appropriate drug
Document the patient's optimal drug concentration before pregnancy. Measure unbound concentrations of phenytoin and valproic acid
Prescribe folate at 4–5 mg/day from before conception
During pregnancy
Offer prenatal diagnosis
Monitor the patient clinically and with serum drug concentrations each trimester, more frequently in patients with poor seizure control or if lamotrigine is used
Adjust dosage in case of generalized tonic–clonic seizures
In sensitive patients a dose adjustment may be justified in response to a significant drop in active drug concentrations also in the absence of seizures
Stress the importance of compliance with prescribed treatment
Monitor drug concentrations closely after delivery and re-adjust dosage if increased during pregnancy

Management during pregnancy

Antiepileptic drug treatment during pregnancy

The optimal management of a woman with epilepsy during pregnancy relies on a close collaboration, with exchange of information between the physician responsible for epilepsy care and the obstetrician (Table 25.5). Treatment with AEDs should be optimized before conception, with the objective to use monotherapy at the lowest effective dosage. Select the AED that is most likely to control seizures (i.e. the appropriate first-line drug for seizure type and epilepsy syndrome). However, accumulating data suggest that valproic acid should be avoided if other equally effective treatment options are available. There is, at present, no simple answer to what the suitable alternative could be for women with idiopathic generalized epilepsies (e.g. juvenile myoclonic epilepsy). Lamotrigine has a reasonable documentation concerning pregnancy outcomes, but the pronounced pharmacokinetic alterations during pregnancy can result in breakthrough seizures. Levetiracetam may be less problematic in this respect, but data on pregnancy outcomes on the other hand are limited. Although as yet we have no signals of major increase in fetal risks with levetiracetam, the data are insufficient to allow firm conclusions. Some prefer carbamazepine. This drug is likely to be effective against generalized tonic–clonic seizures, which is the most important for fetal safety. However, carbamazepine could aggravate myoclonic seizures. Although such seizures are of limited importance during pregnancy, poorly controlled myoclonic seizures can be a major problem after birth when the mother has a newborn infant to care for. Irrespective of which of the alternatives is considered, it is necessary to allow sufficient time before conception to assess its effectiveness.

Treatment should aim at complete control of, in particular, generalized tonic–clonic seizures. Other seizure types are probably less hazardous but may, in some patients, signal an increased risk also for tonic–clonic seizures. Complex partial seizures may also compromise maternal co-operation at delivery.

An attempt to withdraw treatment should be considered in women who plan pregnancy and who have been seizure free for 2 years or more. However, this needs to be assessed individually based on the estimated risk of recurrence and potential consequences thereof. In the case of polytherapy, conversion to monotherapy should be considered, and an attempt to titrate the lowest effective dosage be made. All such major changes should ideally be completed several months before conception to allow a reasonable observation period before pregnancy. It may be useful to document the optimal serum drug level before pregnancy to facilitate interpretation of serum concentration measurements during pregnancy.

Conversion from polytherapy to monotherapy, or changes between AEDs, for the purpose of reducing teratogenic risks,

should not be attempted during pregnancy. At this stage of pregnancy the potential gain is minor compared with the risks associated with such procedures.

The treatment should be monitored more closely during pregnancy than otherwise. This, too, needs to be tailored to the individual but in most cases an assessment each trimester, with a last visit at week 34–36, will suffice. This should include clinical evaluation and drug level monitoring where appropriate. Where phenytoin and valproic acid are used, monitoring the unbound levels is preferred. More frequent drug level monitoring may be justified with lamotrigine and possibly also oxcarbazepine. A decrease in serum levels of AEDs alone does not automatically justify an increase in dosage, but in particular for lamotrigine, declining plasma concentrations have been linked to deterioration in seizure control [29]. The overall clinical state should be assessed and the individual patient's optimal drug concentration and sensitivity to changes in drug levels documented before pregnancy should be taken into account. If a dosage increment was made during pregnancy, serum drug levels should be monitored during the first weeks after delivery, since a dose reduction may be necessary.

Prenatal diagnosis

Women on antiepileptic drugs should be offered the possibility of prenatal testing if elective termination of pregnancy is acceptable. A malformation-directed ultrasound investigation at 16–20 weeks of gestation has a high sensitivity and specificity in the detection of major malformations, including more than 90% of neural tube defects, and a high proportion of cardiac malformations, skeletal defects and orofacial clefts [63]. An ultrasound examination is often offered also at week 33–34 for assessment of intrauterine growth retardation.

Vitamin supplementation

Women with epilepsy considering pregnancy should be prescribed 4–5 mg folate/day, but also informed about the lack of evidence for its efficacy.

Labour and delivery

In general, labour and delivery do not imply any particular obstetric measures. However, delivery should take place in a well-equipped obstetric unit in view of the increased risk of seizures during labour and delivery and the increased risk of neonatal death.

Emergency Caesarean delivery is indicated during labour when seizures induce fetal asphyxia or cause poor maternal co-operation. Intravenous benzodiazepines to the mother are also indicated in such cases.

Puerperium

Stress and sleep deprivation in the puerperium may sometimes adversely affect seizure control. Furthermore, the new responsibilities of the care of the newborn may necessitate special considerations and precautions at home. It is recommended that the mother with epilepsy is given extra support from her partner or others during the first weeks at home, in particular if she is sensitive to sleep deprivation, when seizures are likely to occur. In order to minimize risks to the infant, care for the child, including breastfeeding, is best carried out on the floor, and another person should supervise bathing of the newborn.

Implications for the treatment of women of child-bearing age

The rate of unplanned pregnancies in the general population is high and the first contact with health-care providers is frequently late. These factors are as true for women with epilepsy as they are for anyone else. Therefore, issues related to management during pregnancy will have implications for the treatment of women of child-bearing potential with epilepsy in general. Furthermore, the potential adverse effects of epilepsy and drug therapy on reproductive function, pharmacokinetic interactions with oral contraceptives, as well as developmental toxicity of AEDs, need to be included in the overall risk–benefit equation, which should be the basis for decisions on when and how to treat epilepsy in young women. Thus, it is sometimes reasonable to withhold treatment in new-onset seizures if the indication is weak or ambiguous. If treatment is indicated, it is particularly important in this patient group to aim at monotherapy with the lowest effective dosage. When treatment is initiated in a woman of child-bearing potential, information must be given concerning drug effects on oral contraceptives, when appropriate, as well as potential adverse effects on endocrine reproductive function and implications in relation to pregnancy. The benefits of planning pregnancy should be emphasized. Because of the high rate of unplanned pregnancies, supplementation with folic acid (0.4 mg/day) is reasonable in all women of child-bearing potential who take AEDs. Counselling needs to be iterated at regular intervals. It is also important to inform, at an appropriate age, those women who had onset of their epilepsy as young girls but continue on AEDs beyond puberty.

Based on the considerations above, it is essential to identify young women with epilepsy who are likely to be able to withdraw their treatment without seizure recurrence, and to support them in attempts to taper treatment before they consider pregnancy. Likewise, suitable candidates for epilepsy surgery have the prospect of becoming seizure free, eventually without medication, after a successful operation. Hence, it is of particular value to avoid unnecessary delay in assessment for epilepsy surgery in women of child-bearing potential.

Potential adverse effects on reproductive function should be considered, together with all other relevant properties, when selecting an AED for a woman with epilepsy. The most important property of an AED is its effectiveness in preventing seizures, and for women of child-bearing potential the best choice is the drug that is most appropriate for the seizure type or syndrome. However, the patient should be closely monitored for possible adverse effects on reproductive endocrine function and the treatment reassessed should such side-effects occur. It should also be remembered that drug preferences are likely to change as we gain more information on adverse effects on endocrine function from randomized clinical trials and comparative data on teratogenic effects of different antiepileptic drugs from pregnancy registries.

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26 Epilepsy Counselling

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Introduction

The management of epilepsy presents challenges to clinicians that go beyond the medical aspects of the condition. Some people require assistance in coming to terms with the diagnosis, which can be stigmatizing and associated with psychological problems, reduced social standing and employment difficulties [1]. Some people may feel excluded from society [2]. Most people with the condition, their families and their carers require information about many aspects of epilepsy.

Patient-centred approach

There is a growing awareness of the importance of providing relevant information to people with long-term chronic conditions such as epilepsy. This has been demonstrated in changes in the way that health services are delivered. There is a shift towards a more patient-centred approach, which aims to establish people living with long-term conditions as experts in their particular condition and to empower them to become involved in a collaborative approach to its management [3]. This is demonstrated, for example, in relation to concordance with medication. In the past, people were viewed as compliant with treatment or non-compliant according to the degree to which they followed instructions about how to take their medication. Now, the process of concordance switches the focus from whether the medication is taken and instead focuses on a shared approach to the decision-making process [4].

Whilst some people wish to leave decisions about their treatment to clinicians, many require to be involved in these decisions [5], and initiatives such as concordance require that information is shared in a meaningful way.

Information provision

A review of the literature around the information and counselling needs of people with epilepsy found that people with epilepsy want information on general epilepsy issues, diagnosis and treatment options, medication and adverse effects, seizures and seizure control, prevention of injury, psychological issues, benefits, driving and insurance, employment, prognosis, lifestyle and social issues. People with epilepsy were also found to have counselling needs in relation to anxiety and depression and expressed a need for emotional support [6].

Accessibility of information

Providing information that is relevant and accessible to an individual at any given time is a challenge. Any information aimed at people with epilepsy needs to be accessible and relevant to all people with the condition, including those from disadvantaged backgrounds such as:

- people from various ethnic groups, especially those whose first language is not that of the country in which they reside;
- people with learning disabilities; and
- people with poor literacy skills.

People from these disadvantaged backgrounds are less likely to be able to find relevant information independently. Written information may need to be made available in a variety of languages to suit the local population and to be pitched at an appropriate level using symbols and pictures where appropriate.

How is information given?

Adequate time is needed to provide the full range of information required. In the clinic setting, longer consultations may be required, which can be difficult to achieve in practice. The utilization of specialist epilepsy nurses can help meet the need for longer consultations to encourage dialogue and open discussion of pertinent issues as well as to review clinical issues. The time invested in longer consultations can save time and reduce costs in the longer term by preventing misunderstandings which lead to poorer outcome. Specialist epilepsy nurses also are able to offer continuity of care, which may be important to individuals, allowing for a rapport to be established and trust to be developed [7].

Most people with chronic epilepsy under the care of a neurologist are reviewed at regular intervals as outpatients. Problems can arise between appointments and a telephone advice line, often manned by specialist nurses, is an excellent way of providing assistance. Table 26.1 shows the reasons why people access this type of service within our practice at the National Hospital for Neurology and Neurosurgery. Ninety per cent of the calls received by our service are resolved by the specialist nurses. Consultant neurologist advice is sought for the remaining 10% of calls. Where necessary, changes to treatment can be instigated or outpatient appointments can be brought forward if necessary as a result of calls. Table 26.2 shows the outcomes of calls to our service. Such helplines can be accessed not only by patients but also by their family, carers, GPs, community nurses, hospital

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Table 26.1 Reasons for people calling our telephone advice line service.

Reason for call	Approximate percentage
Seizures worse	30
AED adverse effects	15
General advice (e.g. travel, benefits, employment, safety issues, what to do if medication missed, rescue medication, women's issues, investigations, lifestyle, etc.)	15
Other health problem impacting on epilepsy (e.g. gastrointestinal disturbance)	10
Updating on response to AED adjustment	10
AED supply or prescription problems	5
Clarifying clinic advice and planned changes to AEDs	5
Vagal nerve stimulator-related issues (e.g. adverse effects)	5
Outpatient appointments	5

AED, antiepileptic drug.

Table 26.2 Outcomes of calls to our telephone advice line service.

Outcome	Frequency (%)
Advised	60
Antiepileptic drug adjustment	20
Outpatient appointment brought forward	5
Wait and see	5
Advised GP review	5
Referred to secretary (i.e. change of address or GP details)	5

Table 26.3 Breakdown of callers to our telephone advice line service.

Caller	Frequency (%)
Patient	65
Family member/carer	25
GP	5
Others, e.g. community nurses, social workers, hospital doctors	5

doctors, social workers and others. Table 26.3 shows the breakdown of callers to our service.

Types of information

Information can be given in a variety of formats. Verbal information, given either face to face or via the telephone, has the advantages that understanding can be checked and uncertainty can be quickly clarified, and it can be personalized to an individual's needs. The major problem with verbal information provision is the lack of retention. Techniques to improve retention include the simplification of information by using shorter words and shorter sentences and the repetition of information. Communication can be impaired by anxiety or stress. Verbal information can be reinforced with written information, increasing understanding and improving adherence [8]. Written information can be kept for reference purposes and shared with family or carers.

People with all long-term conditions, including epilepsy, use the internet as a source of information [9]. The internet has much useful information about epilepsy, but quality varies and people should be guided to reputable and reliable sources. In the UK, the NHS maintains a database of information about a variety of medical conditions, including epilepsy, on its website, and some voluntary sector organizations also provide information, much of which can be downloaded via the internet as well as helplines where people can obtain information and advice. People without access to the internet can be supported to obtain information from clinics or other sources such as libraries or voluntary sector organizations in the form of information leaflets, books and DVDs.

Usefulness of information

Counselling at the time of diagnosis

At the point of diagnosis, information is needed about all aspects of the condition but it is neither possible nor desirable to cover all points immediately. The provision of information should be viewed as an ongoing process, with a dialogue established between the clinician and the person with epilepsy. The use of information checklists can be helpful to prompt discussion and to identify what the person with epilepsy would like to know about the condition, as well as keeping a record of what has previously been discussed. Repetition of key points in subsequent reviews with clinicians may help with the retention of information.

Adjustment to a diagnosis of epilepsy is a gradual process for many and can be difficult. Feelings of bereavement may be experienced during the early stages following diagnosis. Grieving for lost hopes and expectations leads to social withdrawal, depression and loss of self-esteem [10]. These problems can stem from a feeling of a loss of control, and this feeling of powerlessness may be coupled with a low mood, which may develop into a reactive depression. Depressive illness may require the assistance of mental health services. Those who are receptive to regular support through counselling benefit from the opportunity to voice fears and emotions openly. The ability to share concerns and fears and to work on difficulties may be sufficient for many and enable the necessary adjustment.

Denial, poor adherence and abuse of alcohol or recreational drugs can compound adjustment difficulties. Problematic adherence to therapy can indicate denial of the diagnosis. It can be helpful in this situation to encourage the weighing up of the detrimental impact on quality of life of a certain course of action against an alternative. Ongoing support may help prevent problems recurring and also identify other difficulties at an early stage.

Issues around taking medication regularly

Once a diagnosis has been established and a decision taken to start treatment with AEDs, information is needed about medication. This includes information about the name of the drug, the dosing schedule and possible adverse effects. People with epilepsy will need to know what to do if adverse effects occur or what to do if their seizure control does not improve with the medication. They will also need to understand at an early stage that AEDs must be taken regularly in order to derive maximal benefit [11].

If medication is not being taken as agreed, the reasons should be explored. For example, people with epilepsy may have problems with memory [12] and may simply forget to take their medication. Sometimes people may not take their medication because they experience adverse effects, and some women may stop taking their medication because they are planning pregnancy and want to avoid the teratogenic effects of AEDs. Some may become complacent if seizures are controlled. Poor adherence with antiepileptic medication is also associated with a poor understanding of the condition [13].

A concordant approach to treatment decisions may be helpful at improving adherence. Open, two-way communication between individuals and clinicians about medicines leads to better adherence, improved satisfaction with care received and greater knowledge of the condition and its treatment [14].

Sometimes, a person can regularly forget to take his/her medication. Establishing the extent of the problem can be difficult. Pill boxes are a cheap and effective prompt in this situation.

Other methods of improving adherence are use of mobile phone alarms to provide reminders, enlisting the support of family members to check that medication has been taken and leaving medication in places where it will be seen during a person's usual routine, such as with a toothbrush or kettle. The carrying of extra medication can be helpful to avoid omitting doses.

Safety and risk considerations

Any individual with epilepsy should be aware of the risks of seizures. The degree of risk depends on the nature and frequency and timing of seizures. The degree of risk acceptable to an individual is a personal choice. Some people with epilepsy have identified precipitants for their seizures and will require advice regarding avoidance of these precipitants. Precipitants vary from individual to individual, but common precipitants include febrile illness, sleep deprivation, psychological stress and excessive alcohol.

People with epilepsy will require advice about situations which can be dangerous if seizures occur. Some are obvious but others are less so. People should be encouraged to perform a mental risk assessment for any activity they are considering.

Safety in the home

Safety advice for the home environment should be tailored to suit each individual's circumstances. Questions to consider include: Does the person live alone? Do they have family support? What are the risks in the event of having a seizure? Is the accommodation accessible by stairs and, if so, is this appropriate and safe? Will a move to more suitable housing be necessary or can the present home be adapted in some way? Are children or other dependants in a vulnerable position if seizures occur? [15]. Referral to occupational therapy may be appropriate and allow for an assessment of the home environment to be made.

A significant danger in the home is the risk of drowning during a seizure whilst bathing. This is an important and preventable cause of death in people with epilepsy [16]. Showering or supervised bathing should be encouraged.

Risks associated with cooking can be reduced by using the back plates on the stove and turning pot and pan handles to the side to reduce the likelihood of being inadvertently knocked during a seizure. Microwave cooking is thought to be safer than cooking on the hob as cooking vessels will be contained, which reduces the risk of scalds and burns, and the timer means it will switch off even if left unattended. Use of sealed containers to carry hot food can also be helpful. A kettle should be filled with the minimum amount of water necessary.

Leisure activities

Many people spend leisure time engaging in activities that may be hazardous if a seizure occurred at that time. Activities such as rock climbing and pot-holing carry obvious risks, and even cycling or swimming can be potentially dangerous if seizures occur. Using a cycling helmet, wearing protective clothing and using designated cycling lanes may reduce some of the risk of cycling. For swimming, it might be advisable for people with epilepsy to limit swimming to pools with clear water, a lifeguard presence and some additional supervision, although the degree and type of supervision will depend on individual factors.

Even when taking precautions it is not possible to remove all risk, and the amount of risk which is acceptable is an individual decision. However, it is important that an individual has made the personal risk assessment with full awareness and understanding of the nature of the risk and has considered ways of reducing any potential risk.

Addressing the risk of death

The possibility of dying as a consequence of epilepsy is a topic that needs to be discussed sensitively. People with epilepsy have a mortality rate which is two to three times higher than that of the general population [17]. Death can occur as a result of a serious seizure-related injury, status epilepticus or sudden unexpected death in epilepsy (SUDEP). Risk can be reduced by measures such as the use of alarms to alert family members to seizures at night. Knowledge of the risk of death in a seizure can improve the adherence to medication, the avoidance of seizure precipitants such as late nights or alcohol, and more risk-averse behaviour.

First aid for seizures

The occurrence of seizures can be distressing and frightening to onlookers, and family and carers should know what to do if a seizure occurs and when to seek medical attention. There is a general lack of awareness about epilepsy among the public, and inappropriate actions taken during seizures can endanger the individual [18]. Information should therefore be given to family and carers about how to manage each type of seizure and the circumstances in which urgent medical assistance should be sought.

Some individuals require the administration of rescue medication to terminate seizures and to prevent the occurrence of status epilepticus. It is good practice in this situation to provide a written plan outlining what medication should be given, how it should be given and what to do if the rescue medication is ineffective. For people with epilepsy living in care homes, the provision of a detailed written plan is of more importance due to staff turnover, and new staff will need clear, concise information that is not open to misinterpretation. Some families and carers will

require training in the administration of rescue medications such as rectal diazepam or buccal midazolam.

Anxiety, social difficulties and overprotection

It has been suggested that there is 'an innate prejudice against epilepsy' rooted in the fear that the person with the condition is always liable to sudden, unpredictable and dramatic losses of motor control or to 'going berserk', something that 'normal' people fear happening to themselves [19]. This fear of going out of control at any time of day or night may be extremely difficult to accept, whether seizures are frequent or not.

The unpredictability of seizures is a particular problem. This may lead to debilitating anxiety. The biggest concerns are around loss of dignity, social isolation and low self-esteem. The involvement of a counsellor with whom they have regular contact presents a forum for patients with epilepsy to examine and discuss these issues.

A natural reaction of family members is to try to protect the person with epilepsy. Setting the boundaries of risk can be difficult, and 'overprotection' is a common reaction. It may in part be the result of feelings of grief or guilt [2]. Overprotection can be harmful to the person with epilepsy and to the family. It may inhibit social life and the forming of independent relationships. It may hinder the development of self-image and a practical attitude towards seizures and risk. It encourages dependency and inhibits psychological coping.

A counsellor should work with the family to overcome issues of overprotection. This can include the setting of realistic educational or employment goals. It can be helpful to meet family members involved in the daily life of the person with epilepsy and to identify areas of specific difficulty. It is important, where possible, to encourage the person with epilepsy to deal with problems rather than to provide protection from them. Encouragement from the counsellor and family will be important if this is to be achieved. 'Learned helplessness' is a common reaction to overprotection and results in a failure to meet potential and unnecessary levels of social withdrawal. Where this has endured to adulthood, it becomes increasingly difficult to reverse and can result in irritability, anger and manipulation, and a situation where the primary disability is the maladaptive illness behaviour.

Employment issues

Employment difficulties are common [1], with economic consequences and adverse effects on self-esteem and mood.

When choosing work, some jobs (e.g. front-line service in the armed services, working on scaffolding, and working as a pilot, etc.) are closed to people with epilepsy. However, there are many types of work that can be undertaken. Considerations for appropriate types of work include the type and frequency of seizures, the presence of a warning and the impact on others in the workplace.

For people in employment who develop epilepsy, the onset of their seizures can signal the end of their career (for instance as a public service vehicle driver). In this situation, people need accurate information about their specific circumstances. People should be encouraged to discuss the implications of the epilepsy with their employer as it may be possible for an alternative job to be found within the same organization. However, it should be recognized that personal identity may be strongly bound up with work, as may financial status, social companionship and sense of purpose.

Communication between employer and employee may be problematic, especially where the employee does not divulge their epilepsy. Fear of having a seizure at work is often reported, and indeed some even report feeling stressed on the journey into work, particularly if they have not disclosed their epilepsy. There is legislation in many countries, such as the Disability Discrimination Act in the UK, which protects people with epilepsy from being discriminated against on the grounds of their epilepsy, although this can be difficult to enforce in practice. However, it can be helpful to inform people of any such legislation to ensure that they know their rights and so that they can seek assistance from the law if necessary.

For people with epilepsy who are unable to find employment or who are unable to continue with their present job, help with interview technique and advice on how to introduce the subject of their seizures can be needed. Assistance from disability employment advisors can also be helpful in assisting people towards appropriate employment or voluntary work where appropriate.

A long period of unemployment should be viewed, where possible, as an opportunity to increase skills through further training and to address difficulties in specific areas.

Women's issues

Women with epilepsy have specific issues around contraception and pregnancy. Information about these issues should be given in advance of the time that the woman becomes sexually active.

Women with epilepsy need to know that some AEDs can impair the efficacy of the combined oral contraceptive pill by inducing hepatic enzymes which speed up the metabolism of the oestrogen component of the pill, putting them at risk of unwanted pregnancy. Women taking enzyme-inducing antiepileptic drugs (AEDs) should be informed of the need to seek specialist family planning advice to achieve effective contraception. Even with appropriate advice, there is a higher risk of contraceptive failure and additional or alternative forms of contraception may be advisable.

Fertility

Epilepsy is associated with reduced fertility [20]. There are various possible social and biological reasons why this may be so. The medication can be a factor, and sodium valproate, for instance, may be associated with polycystic ovary syndrome [21]. Given the issues of fertility, women with epilepsy may wish to consider pregnancy at an earlier age than they would otherwise choose to maximize the chances of conception.

Menstruation and epilepsy

About one in three women with epilepsy experiences clustering of seizures around the time of menstruation [22]. Accurate documentation of seizures with details of the menstrual cycle will help

identify catamenial exacerbations which may have treatment implications.

Pregnancy

There are a number of different issues regarding pregnancy which should be addressed in counselling. The most pressing are the teratogenic effects of maternal drug ingestion on the fetus and the effect of pregnancy on seizure control and the effect of seizures on the fetus. These issues require detailed counselling. Whilst most women with epilepsy will have a normal pregnancy and delivery with no negative effect on their epilepsy and over a 90% chance of a healthy baby, pregnancies in women with epilepsy are considered high risk and require careful management by both neurological and obstetric services [23]. Women with epilepsy should be regularly reminded that their epilepsy should be reviewed by a specialist before they attempt to become pregnant to optimize therapy. Women contemplating pregnancy are advised to take high-dose folic acid until at least the end of the first trimester as this may be protective against neural tube defects. Some women may wish to discuss temporarily discontinuing their AEDs during the first trimester to minimize any risk to their baby. This is possible in some cases, but the advantage of a drug-free period should be balanced against the risk of deterioration in seizure control.

There are various voluntary registers around the world collecting data on the outcome of pregnancies in women taking AEDs, such as the UK's Epilepsy and Pregnancy Register [24], and pregnant women with epilepsy should be encouraged to participate in these registers.

When preparing for the birth of their baby, women should be advised of the importance of continuing to take their AEDs throughout labour to reduce the risk of seizures during labour or in the first 24 h following delivery. Often the labour partner can be entrusted with the job of ensuring this.

Care of the baby

Breastfeeding is generally considered acceptable for women taking AEDs [25], and mothers with epilepsy should be encouraged to choose the feeding method that suits them best.

If a parent with a young baby has seizures, there is a risk to the infant of harm resulting from seizures if, for example, the infant is dropped as a result of a seizure. Parents with young children will therefore need to be advised on safe handling, bathing and feeding. This is particularly important during the immediate postpartum period, as the risk of seizures may be increased as there may be a worsening in seizure control in the context of sleep deprivation, which is common around this time. Parents can be encouraged to reduce risk by changing babies at ground level or not bathing the baby whilst they are unaccompanied by another responsible adult.

Presurgical assessment and support

An increasing number of people with epilepsy who do not achieve seizure control with AEDs are now undergoing resective surgery for the treatment of epilepsy of focal origin [26]. Prior to any surgery, a number of investigations need to be undertaken over weeks or months to establish whether surgery is a suitable therapy. This can be a difficult and stressful time. Counselling is crucial to maintain psychological well-being during the presurgical assessment phase and as a preparation for surgery.

During the presurgical assessment, people are usually hospitalized for some of the investigations. This gives an opportunity for the clinician to discuss key issues without the normal time constraints of outpatient clinics. This is important as prospective surgical candidates need to understand the full ramifications of surgery. It is important, for example, to emphasize the need to continue with AEDs, initially at least, after any surgery. The opportunity to express feelings about the potential future surgery needs to be given, hopes in regard to outcome explored and an assessment made as to how realistic are the goals. The odds of success and the risk of complications of surgery will help individuals come to a rational decision about their suitability for surgery.

Sexual dysfunction

Hyposexuality has been attributed to both epilepsy and AED use. This particular issue is more widely reported in those with temporal lobe epilepsy [27]. Women may find it less difficult to talk about sexual dysfunction than men. Sexual dysfunction can cause considerable emotional turmoil and difficulties within relationships. The frank discussion of such difficulties is often very helpful.

Conclusion

Every person with epilepsy should be assisted towards a good understanding of their epilepsy and its impact throughout their lives. An effective programme of information provision can only have beneficial implications for people with epilepsy, allowing informed decision-making in many aspects of life and enabling appropriate treatment goals. The provision of relevant, good-quality information will also help people to combat the stigma associated with the condition and assist in coping with the condition [28].

Counselling can also be helpful to support people through the psychological difficulties experienced as a consequence of their epilepsy. The need for ongoing support varies and whilst some people may benefit from regular counselling sessions over several months, others may require sessions over a period of years.

The need for the provision of information, advice and psychological support continues throughout the lives of people with epilepsy. Whilst epilepsy may not be an easy condition to live with, providing these services at times when people with the condition really need them will bring relief, optimize outcomes, assist seizure control and facilitate coping with all that a diagnosis of epilepsy brings.

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27 Genetic Counselling in Epilepsy

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Introduction

There have been striking recent advances in the study of the genetics of epilepsy. These carry the promise of elucidating the aetiology of many different epileptic phenotypes, currently considered cryptogenic, in the near future. Although much work towards this goal still lies ahead, current knowledge provides important clues to the pathogenesis and mode of inheritance of various epileptic syndromes. The implementation of this new genetic information in clinical practice has become an important issue in epileptology. Central to this is the process commonly referred to as genetic counselling. The American Society of Human Genetics has defined genetic counselling as a 'communication process dealing with human problems associated with the occurrence, or risk of recurrence, of a genetic disorder in a family' [1].

Genetic counselling aims to help patients and families to:

- comprehend medical data, the diagnosis, the probable course of the disease and the treatment available;
- understand how hereditary factors contribute to the disorder and to appreciate the risk of occurrence of the disorder in specific relatives; and
- choose the appropriate course of action in view of their risks, taking into account the goals and personal morality of the person being counselled.

Genetic counselling therefore involves a diagnostic task, risk assessment and a communicative process.

The pedigree as a diagnostic tool

Accurate genetic counselling is based on reliable diagnoses, and the first principal task for the clinician is to reach as firm a diagnosis as possible.

As familial recurrence is the distinctive feature of most hereditary disorders, the first step towards an accurate diagnosis is a review of the patient's family history. This involves the drawing up of a family tree, which is a powerful tool that can provide the clinician with essential clinical and biological information and which constitutes a permanent and concise record that can be widely interpreted. Pedigrees are drawn by using a universally accepted language that includes the use of symbols indicating sex, disease status and relationships (Fig. 27.1). The pedigree may be used (1) to decide on testing strategies, (2) to distinguish between genetic and non-genetic aetiology, (3) to establish the pattern of inheritance and to calculate risks and (4) to decide on medical screening for unaffected individuals.

The collection of family data should include basic clinical details from both sides of the family for three or four generations. It is advisable to personally examine family members who may be affected or at risk. In doing so, unexpected findings often emerge from relatives with an apparently negative history. A clear diagnosis can be difficult to establish in family members who are deceased. However, detailed information can be obtained by interviewing close relatives, and the exclusion of specific disorders is often possible. Home visits should be considered in selected cases. When collecting family data, it is also important to enquire about consanguinity as a clue to autosomal recessive inheritance. The ethnic and geographical origins of family members should also be carefully investigated in order to detect hidden consanguinity. Unacknowledged paternity (e.g. adoption) should be considered in puzzling situations, as this may exert a confounding effect on segregation of the disease.

Genetic testing is a definitive tool for establishing the diagnosis of an inherited disorder. A genetic test is defined as a laboratory analysis aimed at detecting the alteration of a gene, chromosomal abnormality and DNA variation associated with a genetic disorder. Genetic tests can focus on the analysis of the DNA structure (chromosomes or specific DNA segments) or of gene products (e.g. biochemical assays). Although genetic tests are attractive diagnostic tools, they should be used carefully. Indeed, population screening is recommended for very few genetic disorders, and genetic tests should usually be performed on the basis of precise clinical indications. Moreover, for many genetic disorders, genetic tests have not yet been developed and the accurate analysis of clinical data is the only means of establishing a diagnosis.

Risk assessment

Once a hereditary disorder has been diagnosed, it is possible to estimate any family member's risk of developing the disease. However, as the genetics of many hereditary disorders have not yet been discovered nor appropriate tests devised, the risk of recurrence can often not be calculated exactly and, for many hereditary disorders, will be estimated on the basis of probability. Risk assessment depends on the information available, which is often not complete.

Empirical risks are based on observed data collected through epidemiological studies; these usually provide an acceptable approximation and are widely used for several poorly understood genetic conditions. Population-based estimates are, however, strongly influenced by worldwide variability in incidence and aetiology and may not, therefore, be applicable to all populations.

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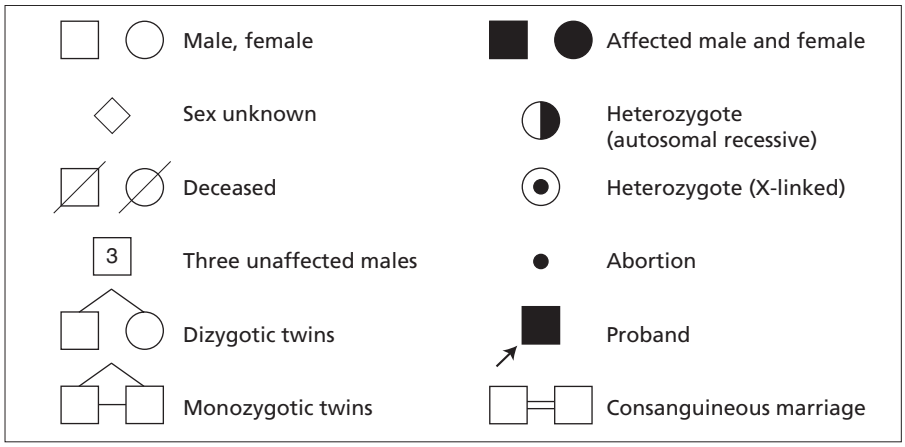

Fig. 27.1 Most common symbols used for drawing a pedigree.

Moreover, empirical risks are frequently revised as new phenotype definitions and more accurate genotype–phenotype correlations become available.

By contrast, genetic risks are defined when the mode of inheritance of the disease is known. To date, such risks may be calculated for disorders that are caused by mutations in a single gene and segregate throughout populations according to mendelian laws. Family members may be classified into clear-cut categories: (1) no risk (i.e. offspring of healthy siblings in autosomal dominant disorders); (2) low risk (i.e. offspring of a potential carrier of autosomal recessive disease); and (3) high risk (i.e. offspring of individuals affected by an autosomal dominant disorder).

Genetic testing

Genetic tests are analyses of human DNA, RNA, chromosomes, proteins or metabolites carried out to detect disease-related genotypes, mutations, karyotypes or molecular phenotypes for clinical purposes. Genetic tests are unique in the sense that they carry information about the biological identity of either the individual or his family ancestors and offsprings. The primary focus of genetic testing is to provide information that contributes to an improvement of health through the prevention or management of disease and illness. Clinical purposes include establishing a clinical diagnosis or prognosis, identifying carriers, predicting risk of disease. Thus, genetic testing should be placed within a specific clinical context, and a variety of conditions must be in place to ensure that the use is appropriate: specialized personnel to perform the test and interpret the results for patients and their families; genetic counselling before and after the test; and follow-up interventions to treat affected patients. Genetic testing may have a beneficial impact on diagnosis, prognosis and treatment. Some patients might be relieved or comforted to have a genetic explanation for their seizures or those of their family members. On the other hand, genetic testing also has potential harmful effects. Genetic information in epilepsy can contribute to psychological distress, discrimination in social life, health insurance and employment [2,3]. To evaluate the utility of a specific test the following parameters should be considered:

- Analytical validity – the ability of the test to appropriately identify a positive sample (sensitivity) and to identify a negative sample (specificity). The analytical validity of a test should be discussed with the laboratory staff before referring the patient.
- Clinical validity – the capability of the test to predict the present or future affection status of the person under investigation.
- Clinical utility – the potential impact of the test on the clinical management of the patient (e.g. surgical interventions, therapeutic approach).
- Ethical, legal and social implications – the potential consequences of the test on stigmatization and discrimination. These, as well as privacy and confidentiality issues, need to be carefully evaluated, particularly when testing should be extended to other family members in order to assess risk.

Clinical genetic tests can be classified into five broad categories, detailed below.

Diagnostic tests

These tests aim to confirm a clinical diagnosis or resolve a differential diagnosis in a affected individual or fetus. Diagnostic tests may:

- save the patient from undergoing other diagnostic procedures which may include risky and/or costly measures;
- direct clinical management, including therapy;
- be of psychological significance even in the absence of a specific therapy; and
- help to manage non-medical but individually important life-spanning aspects.

Carrier identification tests

These tests aim to identify heterozygous carriers in families with a positive history of a recessive genetic disorder or in populations showing a high prevalence of a recessive disease in the context of a community programme. Carrier identification tests may:

- assist individuals in planning future pregnancies; and
- assist, by subsequent counselling, in lowering the disease prevalence in a specific population.

Predictive tests

These tests aim to predict the future health status of a unaffected individual. Predictive tests may be applied to a person showing an elevated risk of developing a disease because of a relevant

family history. These tests are typically used in late-onset disorders. However, predictive tests can applied to the general population as a part of newborn screening. Predictive tests may:

- direct clinical management if a therapy is available to prevent the onset of the disease;
- be of psychological significance even in the absence of a specific therapy; and
- assist individuals in planning future pregnancies.

Susceptibility tests

These tests aim to identify genetic factors increasing the risk of developing a multifactorial disease. In epilepsy, as in many other areas of medicine, the predictive value of these tests is limited and their clinical utility depends on the availability of effective measures that may prevent the disease or its major complications. Susceptibility tests may:

- direct preventing measures in at-risk individuals.

Pharmacogenetics tests

Pharmacogenetics tests are intended to identify genetic factors predicting the response to medicines. Pharmacogenetics tests will enable better prediction of likely outcomes and thus influence the benefit-to-risk ratio of a medicine for patients. Pharmacogenetics tests may:

- predict the efficacy of a specific drug; and
- predict the risk of idiosyncratic reactions of specific drugs and direct therapeutic strategies.

The clinical utility of a genetic test strongly depend on the way testing is integrated into genetic counselling. There are three stages:

1. pre-test genetic counselling;
2. genetic analysis; and
3. post-test genetic counselling.

Pre-test genetic counselling

Pre-test genetic counselling is aimed at:

- gathering pedigree information and identifying necessary clinical documentation;
- making or verifying the diagnosis by history-taking, physical examination and use of information obtained before or during the consultation;
- providing information about the condition which may include its cause, pattern of inheritance, course, complications, outcome and treatment options;
- estimating risk for the counsellee where applicable;
- discussing the medical, emotional and social implications for the individual and family; and
- presenting options, including genetic testing and reproductive options, and assisting with informed decision-making in a non-judgemental/non-coercive manner. The choice of a genetic test should be discussed with the client/family. This includes the nature of the sample required, the appropriateness of the test, the information the test is seeking, the limitations of the test, and the possible implications of the result.

Genetic analysis

Genetic tests may be carried out by using different methodological approaches:

- direct identification of mutations on DNA or retrotranscribed RNA;
- analysis of DNA polymorphisms linked to the disease gene (linkage analysis);
- expression analysis of RNA and protein products; and
- analysis of gene function (i.e. measurement of enzymatic activity or metabolites). Functional tests are included among genetic tests only when the functional abnormalities are unambiguously linked to a specific genetic trait.

Post-test genetic counselling

Post-test genetic counselling is aimed at:

- conveying test results;
- referring to other health professionals as needed;
- considering, and discussing with the counsellee, implications for third parties (i.e. relatives);
- providing education material and/or appropriate references; and
- offering contact with community-based support groups or persons.

Genetic counselling is not just a communication process aimed at informing patients of the risk of recurrence in specific relatives. It should also support patients in taking decisions (e.g. on reproduction) in accordance with their view of life. To this end, genetic counselling should help the patient to understand medical data and clarify any misconceptions.

Diagnosing a specific genetic disorder often implies the involvement of many family members who have been unaware of being at risk. Whether to contact members of extended families should be carefully discussed with patients and, if this is deemed necessary, an 'ad hoc' strategy should be planned.

The evolution of genetic counselling into a process that involves an entire family requires extreme caution. A central principle of genetic counselling is that a non-directive attitude should be adopted. Non-directiveness implies that patients are fully aware of the genetic risks and their consequences and are therefore able to make their own decisions. A totally neutral approach to genetic counselling cannot realistically be achieved; nevertheless, it must be emphasized that counsellors should not aim to provide solutions to critical questions concerning patients' lives.

Mode of inheritance of genetic disorders

It has long been known that many phenotypic characteristics of living beings are transmitted according to Mendel's laws. In Mendel's model, genetic factors segregate from parents to offspring as independent and unaltered units, and phenotypes result from the interaction of variants (alleles) of these discrete units according to hierarchical relationships (dominant versus recessive).

Mendel developed his model of the transmission of phenotypic traits just by observing peas in a garden. This discovery provides a valid basis for the understanding genetic inheritance. However, it has been subsequently realized that mendelian laws are simplified, and that the segregation of phenotypes in humans is more complicated. We now know that Mendel's units (genes) lie along

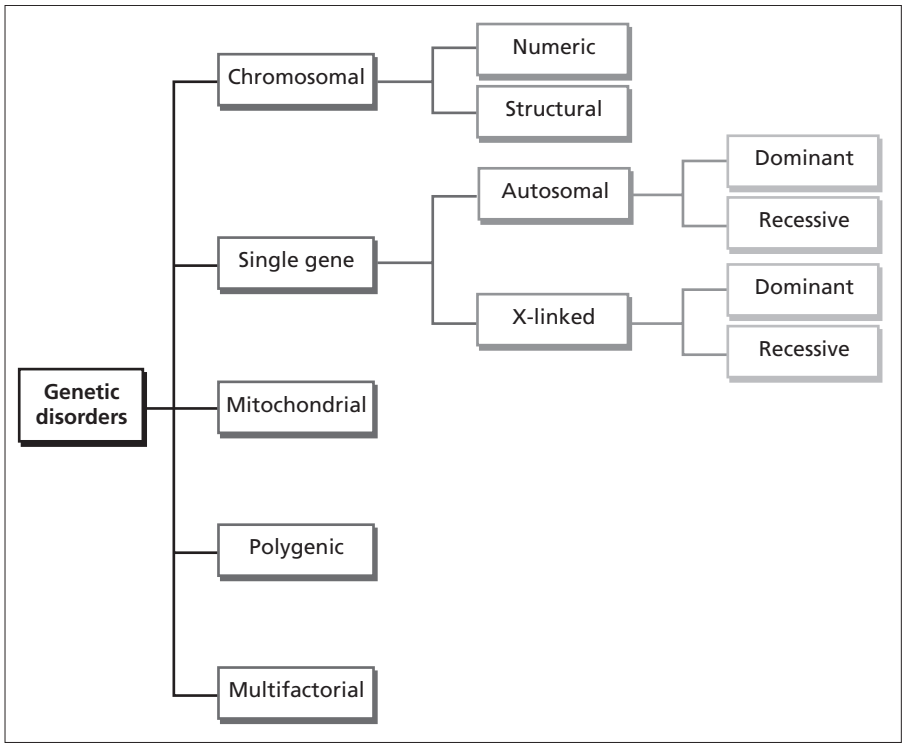

Fig. 27.2 Classification of genetic disorders.

chromosomes in close proximity and that DNA is transmitted in segments containing tens to hundreds of genes. Genes are not, therefore, always independently transmitted. We also have learned that genes sometimes undergo mutations during transmission (i.e. *de novo* mutations and dynamic mutations due to trinucleotide repeat expansions) instead of being maintained unaltered. Moreover, most molecular pathways and cellular functions are regulated by very complex systems that may involve hundreds of genes. Thus, most cellular, physiological and clinical phenotypes frequently result from the interaction of several genes and not from single genes. The presence of genes on the X chromosome and maternally inherited mitochondrial DNA add further complications to the analysis of the transmission of clinical phenotypes.

In accordance with the above considerations, we may class inheritance patterns as: (1) chromosomal inheritance; (2) single-gene mendelian inheritance; (3) X-linked inheritance; (4) mitochondrial inheritance; (5) complex inheritance (Fig. 27.2). Moreover, it should be stressed that a genetic disorder is not always a transmitted condition. Although several cellular mechanisms strive to maintain DNA structure and sequence unaltered during the cell cycle, mutations and chromosomal anomalies can take place during gametogenesis (so-called *de novo* mutations). When *de novo* mutations occur, clinical phenotypes manifest as sporadic events in families with an unremarkable history, and in these families no inherited risk is found. *De novo* mutations usually result in severe phenotypes and represent a persisting reserve of otherwise selectively eliminated conditions.

Chromosomal inheritance

The correct segregation of genes through meiotic division is a critical step for the survival of a species. In humans, this function is carried out by 23 pairs of chromosomes (22 autosomal pairs and two sex chromosomes), each harbouring tens to thousands of genes. In chromosomal disorders, chromosome segments are missing from or added to the normal set, leading to the absence or duplication of various genes and to composite phenotypes. The most common clinical signs of chromosomal disorders are dysmorphic features and mental retardation, resulting from an unbalanced dosage of different genes. The severity of the phenotype may, however, vary according to the type and number of genes involved.

Most chromosomal disorders are associated with chromosomal abnormalities occurring *de novo* and thus the occurrence of the clinical phenotype is a sporadic manifestation. More rarely, chromosomal disorders (e.g. balanced translocations) arise from healthy carriers of balanced and phenotypically silent rearrangements. The presence of multiple miscarriages and/or mental retardation in a family may be suggestive of such parental rearrangements. The recurrence risk mainly depends on the type and size of the rearrangement, the chromosome involved and the sex of the carrier (the father being at increased risk) (Table 27.1).

Mendelian inheritance

Mendelian inheritance applies when mutations in a single autosomal gene are sufficient to determine a clinical phenotype. According to the type of genes and mutations implicated, we find autosomal recessive (AR) disorders, in which both copies of the disease gene have to be mutated in order to express a phenotype, and autosomal dominant (AD) disorders, in which a single copy of the gene is mutated.

- Autosomal recessive disorders are characterized by healthy carriers who are heterozygous for a mutated allele and affected individuals who have inherited two mutated alleles from carriers. Affected individuals may be homozygous, or what is termed

Table 27.1 Risk for relatives of proband for different disease modes of inheritance.

Inheritance	Risk to family members of a proband			
	Parents	Siblings	Offspring	Other family members
Chromosomal	Relative risks depend upon specific chromosomal rearrangement			
Autosomal recessive (AR)	Obligate heterozygotes Heterozygotes are asymptomatic	*At conception:* 25% chance of inheriting both disease alleles and being affected 50% chance of inheriting one disease-causing allele and being a carrier 25% chance of inheriting both normal alleles and being unaffected *Normal sibs:* 2 out of 3 chance of being a carrier	>99% heterozygotes (healthy carriers) Very rarely homozygous (affected) (only if husband/wife is heterozygous or affected) [frequency heterozygous in the general population × 0.5 (risk of transmitting the disease allele)] + [frequency homozygous in the general population × 1 (100% risk of transmitting a disease allele)]	Maternal and paternal relatives are at risk of being carriers
Autosomal dominant (AD)	One parent of the proband has the same disease-causing allele as the proband; that parent may or may not have symptoms depending on the penetrance of the disease allele	50% risk of inheriting the disease allele 50% risk of developing the disease for fully penetrant genes <50% risk of developing the disease for incomplete penetrant disease alleles (0.5 × penetrance rate). A proportion of sibs [0.5 × (1 – penetrance rate)] may carry the disease allele without expressing the phenotype	50% risk of inheriting the disease allele 50% risk of developing the disease for fully penetrant disease alleles <50% risk of developing the disease for incomplete penetrant disease alleles (0.5 × penetrance rate). A proportion of offspring [0.5 × (1 – penetrance rate)] may carry the disease allele without expressing the phenotype	
X-linked recessive	Mothers are obligate carriers. Mild symptoms of the disease may manifest	Males: 50% chance of inheriting the disease allele and of being affected Females: 50% change of being carriers with no or mild symptoms, 50% chance of not inheriting the disease allele and being normal	All daughters will be carriers Sons will not inherit the mutant allele, will not have the disease and will not pass it on to their offspring	Maternal aunts and their offspring may be at risk of being carriers or affected depending upon their gender
Mitochondrial	mtDNA deletions generally occur *de novo* and thus cause sporadic disease with no significant risk to other family members mtDNA point mutations and duplications may be transmitted through the maternal line The mother of a proband usually has the mtDNA mutation and may or may not have symptoms The father of a proband is not at risk of having the disease-causing mtDNA mutation	The risk to the sibs depends upon the genetic status of the mother. If the mother has the mtDNA mutation, all sibs are at risk of inheriting it	A male does not transmit the mtDNA mutation to his offspring A female harbouring a mtDNA mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability amongst sibs within the same nuclear family	The proband's grandmother and her descendants are at risk
Complex	Empirical risks should be deduced from disease-specific epidemiological studies			

mtDNA, mitochondrial DNA.

compound heterozygous, when each allele contains a different mutation. Autosomal recessive inheritance usually manifests as a sporadic event within pedigrees in which carriers are phenotypically normal. At conception, the sibs of probands have a 25% chance of inheriting both disease-causing alleles and being affected, a 50% chance of inheriting one disease-causing allele and being a carrier, and a 25% chance of inheriting both normal alleles and being unaffected. The normal sibs of a proband have a 2 out of 3 chance of being a carrier. The offspring of a proband are all obligate heterozygotes (Table 27.1). Consanguinity may significantly increase the risk of an autosomal recessive disorder being expressed, since a single ancestral mutation could be transmitted along both paternal and maternal lineages (Fig. 27.3).

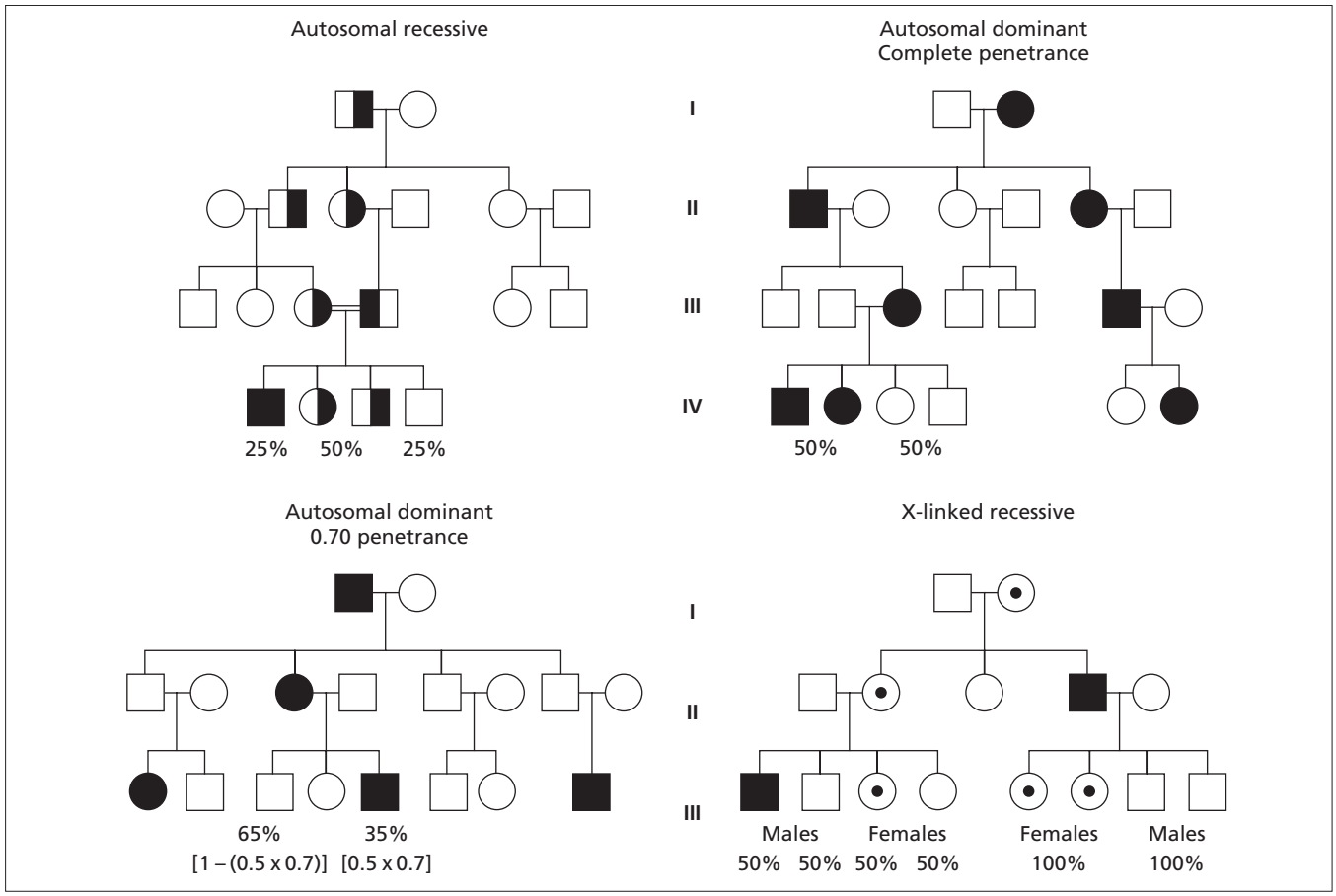

Fig. 27.3 Pedigrees showing different single-gene patterns of inheritance and relative risks for offspring.

- Autosomal dominant disorders are characterized by vertical transmission of the disease through generations. Affected individuals present a 50% risk of transmitting the phenotype to their offspring (Table 27.1). Autosomal dominant inheritance is typically recognized in large multigenerational pedigrees showing a high density of affected cases (Fig. 27.3).

By definition, single-gene mendelian disorders are homogenous traits; transmission of the disease is defined by Mendel's laws and phenotypes usually show little variability among affected individuals.

However, it is well known that several disorders classified as mendelian – mostly in the autosomal dominant category – show a certain degree of variability in expression of clinical features. This can be the result of *incomplete penetrance*, in which a proportion of individuals carrying the mutation(s) do not manifest the phenotype. The onset of clinical symptoms and variation in the severity of the phenotype also occur (Fig. 27.3). Recent advances in genetic research have revealed that the variability in expressivity found in some single-gene mendelian traits is definitively influenced by other genes. Since the phenotype is mostly determined by mutations in a single gene, we may define these traits as major-gene disorders. For the sake of simplicity, these are included in the single-gene disorder category, as the pattern of inheritance (so-called oligogenic inheritance) overlaps to a great extent with mendelian inheritance.

X-linked inheritance

When mutations occur in genes lying on the X chromosome, a peculiar mode of inheritance is found because of the difference in gene dosage between males and females. X-linked mutations are usually transmitted from heterozygous healthy females (carriers) to 50% of their offspring. Male offspring will develop the disease, since they lack the second normal copy of the gene (hemizygosity), whereas females will be the healthy carriers. A distinctive feature of X-linked inheritance is the absence of male-to-male transmission of the disease (since the Y chromosome is always transmitted). Since the disease is transmitted by normal carriers, we may define most X-linked disorders as recessive traits (Table 27.1 and Fig. 27.3).

It should, however, be stressed that use of the recessive–dominant dichotomy should be cautious, as female carriers can show a variable phenotype, with usually mild abnormalities, that is the expression of the random inactivation of one X chromosome. This phenomenon (also called lionization) occurs in a female in whom one X chromosome (either the maternally or paternally derived X) is randomly inactivated in early embryonic cells and this inactivation is carried forward by all cells descended from these cells. This is an epigenetic change, in other words an inheritable change in gene function without a change in the sequence of the DNA. X inactivation can occur in males with

syndromes (e.g. Klinefelter's) who have more than one X chromosome. Moreover, some X-linked genes show a clear dominant effect and heterozygous females express the full phenotype. Furthermore, in rare X-linked dominant syndromes, hemizygosity is lethal in males.

It is noteworthy that the counterpart of X-linked inheritance does not exist in practice, since no genes responsible for serious diseases are known to be mapped on chromosome Y. For those rare disease genes that are mapped on both sex chromosomes (within the so-called pseudoautosomal regions), the pattern of inheritance is typically mendelian.

Mitochondrial inheritance

In human cells about 1% of the DNA is contained within mitochondria as small circular genomes. The mitochondrial DNA (mtDNA) of each individual is derived from maternal mitochondria (in humans, sperm does not contribute to the initial set of mitochondria) and to replicate independently from nuclear DNA.

Mitochondrial DNA harbours 37 genes encoding for transfer RNA (tRNA) and proteins that are involved in mitochondrial function. Mitochondrial genes undergo a variety of mutations, leading to disorders that typically affect the central nervous system, heart, skeletal muscle, endocrine glands and kidneys; transmission is always from females, no transmission being observed from males (Table 27.1). Because of the maternal origin of mtDNA, a peculiar inheritance pattern is found (Fig. 27.4).

A further distinctive feature of these disorders is phenotypic variability in both the severity and progression of disease and the age of onset. Furthermore, individuals with no clinical manifestations may transmit the disease. The clinical heterogeneity is because the proportion of mutated mtDNA varies in different cells; in some cells, all mitochondria carry the mutated mtDNA (homoplasmy), while in others only a fraction of mtDNA is mutated (heteroplasmy). Thus, the variable expression of the disease is strongly influenced by the amount and the tissue distribution of mutated mtDNA. The proportion of offspring possibly affected is therefore variable and cannot be determined by any rule.

Since several genes involved in mitochondrial function are localized in nuclear DNA, it should be emphasized that mitochondrial inheritance does not apply to all mitochondrial disorders.

Complex inheritance

Most common disorders show a complex aetiology that includes multiple genetic and environmental factors. In these disorders, a single gene is not sufficient to cause the disease by itself, but increases the risk (i.e. carries genetic *susceptibility*). The disease may develop when other genes (polygenic disorders) or environmental factors (multifactorial disorders) are superimposed on a genetic predisposition. As a result, these conditions may show a familial tendency but do not fit into a clear inheritance pattern (Fig. 27.4).

Distinctive epidemiological features of genetically complex disorders are (1) increased clinical concordance among monozygotic twins; (2) increased risk for close relatives of affected individuals, rapidly decreasing for more distant relatives; and (3) pedigrees showing a sparse aggregation of affected cases. Recurrence risks are usually based on empirical data, indicating the risk for relatives of affected individuals as a function of the degree of relationship and of the presence of multiple affected cases in family (Table 27.1). For many complex disorders, large and dense pedigrees do occur, showing that a subset of occasional families carry rare genetic variants which have a major effect. Recognizing these mendelian subsets is crucial to identifying high-risk individuals.

Genetic counselling in epilepsy: approaching a heterogeneous disorder

Epilepsy is a very heterogeneous disorder, which is manifested in a variety of clinical signs and which has multiple causes. Generally speaking, humans may have a seizure or develop epilepsy as a result of acquired and/or genetic causes.

In the *symptomatic epilepsies*, the seizures are caused by neurological damage. These conditions are commonly acquired during postnatal life, and causes include head injury, cerebrovascular disease, central nervous system infections and brain tumours or degenerative disorders. There are, therefore, few influenced by the genetic background, although the genetic make-up can affect an individual's susceptibility to developing epilepsy; for instance,

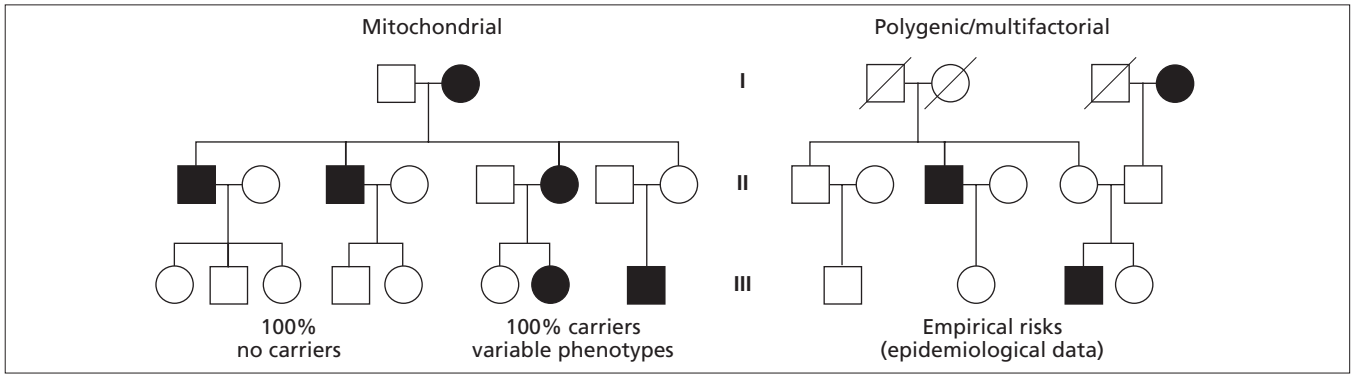

Fig. 27.4 Pedigrees showing complex patterns of inheritance.

the rate of post-traumatic epilepsy after head injury has been found to be greater in patients with a family history of epilepsy. In rare cases, symptomatic epilepsy may arise from structural brain lesions or altered metabolic states that are associated with specific inherited disorders (e.g. tuberous sclerosis, neuronal ceroid lipofuscinoses).

By contrast, individuals with *idiopathic epilepsies* suffer recurrent unprovoked seizures without any detectable neurological or metabolic abnormality. Epidemiological studies have shown that genetic factors strongly contribute to the aetiology of idiopathic epilepsies [4]. The mode of inheritance of idiopathic epilepsy is, however, highly variable and includes mendelian, polygenic and multifactorial traits. In recent decades, a great effort has been made to narrow down phenotypes in the idiopathic epilepsies according to clinical details such as age of onset, type of seizures and EEG findings. Epileptic syndromes have been defined according to unique clusters of signs and symptoms, and then grouped into extended classifications [5,6]. On this basis, epidemiological studies have been undertaken in an attempt to provide empirical estimates of recurrence risks for each phenotypic trait. In epilepsy, most of the available data for genetic counselling are derived from this exhaustive workup. Although many patients do not fit any proposed phenotypic class, and clinical classification may have little aetiological value, it is important to approach the current classification as a diagnostic scheme on which empirical risks for recurrence have been calculated. Thus, by definition, relatives of probands affected by idiopathic generalized epilepsy show an increased risk of developing generalized epilepsy. By contrast, relatives of individuals showing temporal lobe epilepsy with hippocampal sclerosis are not considered to be at increased risk.

The classification of some genetically determined forms of epilepsy is likely to undergo extensive reappraisal, with significant implications for clinical diagnosis and genetic counselling. Dissecting the complex aetiology of different forms of epilepsy will have considerable impact on genetic counselling by providing reliable genetic tests for diagnosis and more accurate estimation of risks. A further issue, which is critical in relation to genetic counselling, is the clinical variability observed for many epileptic traits. Thus, although it is often possible to estimate a recurrence risk for a specific disorder, it may be impossible to estimate severity of the disease. Whilst this question may be of little significance when clinical variability encompasses a benign spectrum, it becomes very important in conditions in which severe phenotypes occur. A deeper knowledge of the aetiological factors involved in such disorders and the development of appropriate tests are crucial to addressing this issue.

Idiopathic epilepsies

In epilepsy, the term idiopathic refers to clinical conditions in which seizures manifest as unique symptoms in the absence of structural brain lesions or other neurological dysfunctions. Most of these conditions cause generalized epilepsy, although several focal forms of epilepsy are now also recognized to be genetically determined [7]. A distinctive feature of most idiopathic forms is the age dependency of clinical manifestations. Seizures and EEG abnormalities are observed in a specific age window, usually within the first two decades of life, as a result of a complex interaction between brain maturation and inherited factors. The inheritance pattern of idiopathic epilepsy is heterogeneous; the most common forms show a complex mode of inheritance, indicating the involvement of several genes and environmental factors, whilst other phenotypes are inherited as single- or major-gene traits. The age dependency of idiopathic forms of epilepsy can complicate diagnosis in adults and make the recognition of mendelian patterns of inheritance difficult; and the incidence of single- or major-gene traits in the general population is probably underestimated. In view of the above considerations, idiopathic epilepsies can be subdivided into mendelian, complex and sporadic forms.

Mendelian epilepsies

Seven syndromes have so far been identified as having mendelian inheritance: benign familial neonatal seizures (BFNS), benign familial infantile–neonatal seizures (BFNIS), benign familial infantile seizures (BFIS), generalized epilepsy with febrile seizures plus ($GEFS^+$) syndrome, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), autosomal dominant partial epilepsy with auditory features (ADPEAF) and benign adult familial myoclonic epilepsy (BAFME) (Table 27.2). These phenotypes have been clearly characterized at the clinical level and are consistently recognized worldwide. In addition, several epilepsies with mendelian inheritance have been reported in single families, and additional studies will be necessary to assess whether these traits have importance in the general population.

Benign familial neonatal seizures

Seizures are the most frequent neurological events in newborns. In most cases, seizures are the result of an acute severe metabolic or structural cerebral disturbance. A small number of neonatal seizures, however, show no obvious precipitating factors and have a benign prognosis and a family history; some of these cases are defined as BFNS. Distinctive clinical features of BFNS include the occurrence of brief focal or generalized seizures with an onset between 2 and 4 days of life, and which spontaneously remit within a few weeks. Seizures usually start with a tonic posture, ocular signs (staring, blinking or gaze deviation) and apnoea and progress to clonic movements and motor automatism [8]. The ictal EEG usually shows a characteristic sequence of bilateral flattening for 1–5 s, followed by bilateral discharges of slow waves and spikes lasting 1–2 min. The cortical spread may vary between left and right among seizures, resulting in asymmetric motor signs. BFNS was originally classified as a generalized epilepsy but it has been recently included among the partial epilepsies [6]. However, in view of the immaturity of the neonatal brain, such a rigid classification is inappropriate. Seizures are usually controlled by phenobarbital; phenytoin and valproate are occasionally used in non-responsive patients. Psychomotor development is normal, although about 10–15% of patients will develop febrile or non-febrile seizures later in childhood or adolescence [9]. The pattern of inheritance is typically autosomal dominant with high penetrance (around 85%), indicating involvement of a single gene. Mutations in the voltage-gated potassium channel α-subunit genes *KCNQ2* and *KCNQ3* have been identified as responsible for BFNS, and several mutations which result in either

Table 27.2 Mendelian epilepsies.

Disease	Age at onset	Suggestive clinical and EEG features	Mode of inheritance	Gene(s)
Benign familial neonatal seizures	2–4 days	Tonic posture, ocular signs, apnoea evolving into clonic movements and motor automatisms. Ictal EEG: bilateral flattening of the EEG followed by bilateral discharge of slow waves and spikes	AD, 0.85 penetrance	*KCNQ2*, *KCNQ3*
Benign familial neonatal–infantile seizures	2 days to 6 months	Focal seizures originating from posterior regions with secondary generalization and prominent motor manifestations	AD, high penetrance	*SCN2A*
Benign familial infantile seizures	4–7 months	Seizures usually in clusters: psychomotor arrest, slow deviation of the head and eyes, diffuse tonic contraction, cyanosis and limb jerks. Ictal EEG: fast activity in occipitoparietal areas and secondary generalization	AD, high penetrance	Unknown
Generalized epilepsy and febrile seizures plus (GEFS$^+$) syndrome	1–9 years (mean 1.5)	Very frequent febrile seizures lasting beyond 6 years and/or followed by generalized tonic–clonic seizures. Occasional recurrence of afebrile generalized myoclonic, absence and atonic seizures	AD, 0.80 penetrance	*SCN1A*, *SCN1B*, *GABRG2*
Autosomal dominant partial epilepsy with auditory features	8–50 years (mean 20)	Focal seizures mostly with secondary generalization, auditory auras, seizures triggered by noise	AD, 0.70 penetrance	*LG1*
Autosomal dominant nocturnal frontal lobe epilepsy	1–55 years (mean 14)	Nocturnal motor seizures: moans, extension and abduction of arms, axial rocking, grabbing, oral automatisms, aura. Ictal EEG: fast bifrontal rhythm	AD, 0.80 penetrance	*CHRNA4*, *CHRNB2*
Benign familial adult myoclonic epilepsy	18–45 (mean 30)	Tremulous finger movements and/or myoclonus of the extremities and rare generalized tonic–clonic seizures. Photic sensitivity. Enhanced long-loop C-reflex. Ictal EEG: generalized spikes or poly-spikes and slow-wave complexes	A, high penetrance	Unknown

AD, autosomal dominant.

a truncated or altered protein have so far been described [10,11].

Genetic testing for BFNS includes the mutational screening of *KCNQ2* and *KCNQ3* by using genomic DNA from patients. This is costly and should be undertaken only when the clinical diagnosis is highly suggestive. Familial clustering of neonatal seizures constitutes a distinctive marker of the syndrome, although it may be not easily recognized because of the absence of clinical and EEG signs in adult individuals. For genetic counselling, the risk estimate is typical of any autosomal dominant single-gene disorder with high penetrance, with a 50% risk of transmission for offspring or siblings of affected individuals.

Benign familial neonatal–infantile seizures

Benign familial neonatal–infantile seizures were originally described by Kaplan and Lacey as an autosomal dominant epileptic trait characterized by clusters of seizures developing between 2 days and 3.5 months and spontaneously remitting after the first year of life and with a benign outcome [12]. This phenotype was under-recognized for a long time and only recently has the genetic aetiology of this disorder been dissected and its phenotypic spectrum further delineated [13]. BFNIS is characterized by focal seizures usually originating from posterior regions with secondary generalization and prominent motor manifestations as described for BNFS and BFIS. Seizures onset between 2–3 days and 6 months, usually around the ages of 2–3 months. The diagnosis of BFNIS should be considered when seizures start before the age of 6 months, particularly if a combination of neonatal and early-infantile seizures is found in the family. Genetic studies have revealed that BFNIS is due to mutations affecting *SCN2A*, the gene encoding the α_2-subunit of the neuronal voltage-gated sodium channel [13–15]. The expression of mutant channels in cultured hippocampal neurons has revealed that these mutations increase both subthreshold and action Na^+ currents causing hyperexcitability [16]. So far, only a few families with BFNIS have been reported. However, all have *SCN2A* mutations and BFNIS is a benign age-related trait. The mutational screening of *SCN2A* has limited utility in the clinical management; however, it may be attempted to obtain the confirmation of the diagnosis in highly suggestive families.

Benign familial infantile seizures

Benign familial infantile seizures were described in 1992 as an autosomal dominant disorder characterized by partial seizures occurring between 4 and 7 months and spontaneously remitting at about 18 months, and with a benign outcome [17]. Seizures are brief (usually less than 1 min), occur mainly in clusters of 4 to 10 per day and last for a period of 2–4 days. Isolated seizures may sporadically precede clusters. Clinically, seizures are highly stereotyped among patients, and include psychomotor arrest,

slow deviation of the head and eyes to one side, diffuse tonic contraction, cyanosis and limb jerks starting unilaterally and evolving into synchronous or asynchronous bilateral manifestations. Depending on the seizure, the head and eyes may be turned to either the right or left side. Ictal EEGs show a fast activity originating in the occipitoparietal areas of one hemisphere and then spreading over the entire brain and increasing in amplitude. Phenobarbital therapy is usually effective and brings seizures under control within 2 days. Interictal EEG and psychomotor development are normal and no increased risk of developing febrile or non-febrile seizures is observed in later life.

The mode of inheritance of BFIS is typically autosomal dominant, although occasionally the disease is transmitted from apparently healthy individuals. It is not clear whether this is due to incomplete penetrance or difficulties in collecting a reliable history from adult individuals.

Non-familial cases with idiopathic seizures with onset within the first year of age, spontaneously remitting and showing overlapping clinical features with BFIS, have been described [18]. Clinical dissection of benign infantile seizures has been attempted in order to identify any phenotypic variants that may underlie the observed difference in inheritance pattern. In some (but not all) sporadic cases, EEG recordings have demonstrated a temporal lobe onset, suggesting a different pathogenesis.

Extensive family studies led to the localization of two different BFIS genes on chromosomes 19q and 2q. Genetic heterogeneity is further emphasized by families in which the disease is not linked to either 19q or 2q, thus suggesting the presence of at least a third BFIS gene [19–21]. The complexity of the BFIS syndrome is, moreover, highlighted by recent reports of familial cases of infantile seizures and paroxysmal choreathetosis (ISCA syndrome) [22]. In ISCA, typical epileptic manifestations of BFIS are associated with involuntary movements that occur spontaneously (dystonic type) or are induced by movement (kinesiogenic type), exertion or anxiety. In familial ISCA, both choreathetosis and seizures show reduced penetrance and thus the disorder may manifest as an epileptic, choreoathetotic or combined phenotype. Whether BFIS and ISCA constitute different clinical manifestations of the same genetic defects is currently unclear. Both ISCA and BFIS have been linked to chromosome 16p in some families, suggesting a genetic overlap between these two syndromes [23]. The identification of *SCN2A* mutations on chromosome 2q24 in BFNIS syndrome and in some families with typical BFIS [13,24] confirmed that these syndromes show a significant genetic and clinical overlap. Due to the rare occurrence of *SCN2A* mutations in BFIS, the screening of this gene is usually negative and should not be routinely requested.

Generalized epilepsy with febrile seizures plus syndrome

The GEFS$^+$ syndrome was originally described in Australia and has since been reported worldwide in many families. The epilepsy is inherited as an autosomal dominant trait [25]. Clinical features include febrile seizures and various forms of other seizures, mostly generalized, but more recently non-febrile focal seizures have been also recognized to occur (and for this reason, it has been suggested that the syndrome be renamed genetic epilepsy with febrile seizures plus. The febrile seizures last beyond 6 years of age (hence the term febrile seizures plus) and are frequently followed by generalized non-febrile seizures of various types, such as myoclonic, absence and atonic seizures. In GEFS$^+$ families, however, about 40% of affected individuals show typical febrile seizures without further seizures, reflecting variable expression.

The pattern of transmission is typically autosomal dominant and a single major gene is thought to determine the phenotype. Incomplete penetrance and variable expression of the disease suggest that minor alleles might influence the phenotype. So far, three major genes have been associated with the GEFS$^+$ syndrome: voltage-gated sodium channel subunits α_1 and β_1 genes (*SCN1A* and *SCN1B*, respectively) [26,27] and the $GABA_A$ receptor subunit γ gene (*GABRG2*) [28]. GEFS$^+$ can be difficult to distinguish from febrile seizures or common forms of idiopathic generalized epilepsy if the familial clustering is missed. The occurrence of febrile seizures plus is an important diagnostic clue. Genetic counselling should take into account the variability of the disease, which may manifest with severe (i.e. myoclonic astatic epilepsy) or mild phenotypes [29]. Incomplete penetrance (about 80%) lowers the risk for relatives of probands compared with fully penetrant traits.

The fact that the GEFS$^+$ genes so far identified account for only about 20% of the GEFS$^+$ phenotypes indicates that other genes are involved. The screening of GEFS$^+$ genes is a costly task and should be undertaken only to confirm diagnosis when febrile plus seizures are consistently found in different family members.

Autosomal dominant nocturnal frontal lobe epilepsy

Frequently misdiagnosed as sleep disorder, ADNFLE is characterized by clusters of brief nocturnal motor seizures that begin at different ages – usually in childhood – and may persist throughout adult life [30]. Seizures are brief – usually 30–40 s – and occur in clusters of up to 20 attacks during light sleep. Clinical manifestations include moans, extension and abduction of arms, axial rocking, grabbing at people or objects and oral automatisms. Individuals may experience an aura associated with tonic and hyperkinetic motor activity. The ictal EEG shows generalized high-voltage slow and sharp activity, followed by fast bifrontal rhythm and then by a burst of poly-spikes and slow waves with sudden cessation. Intrafamilial variability in the severity of symptoms is frequently observed. Interictal and psychomotor development are normal. Carbamazepine is usually effective in controlling seizures.

Autosomal dominant nocturnal frontal lobe epilepsy is an inherited autosomal dominant condition with 80% penetrance. Seizures may be difficult to detect in family members, and nocturnal motor manifestations are frequently misdiagnosed as sleep disorders such as nightmares, hysteria and paroxysmal dystonia. Clinical heterogeneity further complicates clinical diagnosis. The presence of non-familial cases suggests a composite aetiology for nocturnal frontal lobe epilepsy. Mutations in the neuronal acetylcholine receptor α_4- and β_2-subunit genes (*CHRNA4* and *CHRNB2*) have been identified in ADNFLE patients [31,32]. More recently, mutations of the gene encoding the α_2-subunit of the acetylcholine receptor – *CHRNA2* – have been identified in a single family with autosomal dominant

inheritance, confirming the highly heterogeneous genetic aetiology of this phenotype [33]. Analysis of ADNFLE genes demonstrated a *de novo* mutation in only one of several patients affected by non-familial nocturnal frontal lobe epilepsy, thus suggesting that other factors are involved in sporadic nocturnal frontal lobe epilepsy [34].

In ADNFLE, as in all mendelian forms of epilepsy, genetic counselling should first focus on clinical diagnosis and the recognition of familial clustering. The screening of *CHRNA4* and *CHRNB2* may then be attempted when the transmission pattern supports autosomal dominant inheritance. *CHRNA6* mutations have been identified in only a single family so far and the screening of this gene should not be attempted for diagnostic purposes. Likewise, current data do not suggest extending the test to sporadic cases.

Autosomal dominant partial epilepsy with auditory features

Autosomal dominant partial epilepsy with auditory features is a syndrome which has been recently delineated by Ottman and colleagues [35,36], and is now recognized to have a worldwide occurrence. The distinctive clinical features are autosomal dominant mode of inheritance with incomplete penetrance, an onset of seizures spanning childhood and adulthood but usually in adolescence, the occurrence of rare focal seizures mostly with secondary generalization, the absence of structural brain abnormalities and a benign evolution. The clinical hallmark of this phenotype is the auditory aura occurring during focal seizures and suggesting a lateral temporal seizures onset. Different types of auras such as visual or aphasic may also occur, which confirm the localization to the lateral temporal lobe [and thus the alternative name of autosomal dominant lateral temporal lobe epilepsy (ADLTE) has been suggested [37]]. The interictal EEG is not usually contributory, although in some patients mild temporal EEG abnormalities occur. In addition, the seizures may be triggered by sudden external stimuli, in particular noise [38]. Genetic studies led to the identification of mutation in leucine-rich glioma-inactivated 1 (*LGI1*), a gene originally described to be deleted in gliomas [39]. *LGI1* mutations are almost invariably associated with familial forms of this condition, and only a single *de novo* mutation has been identified in a sporadic case affected by idiopathic partial epilepsy with auditory features [40]. In addition, the analysis of mutations in this gene in patients with common forms of temporal lobe epilepsy has been consistently negative, indicating that *LGI1* mutations are specific for ADPEAF and are not a common genetic factor for temporal lobe epilepsy [41]. Mutations may lead to premature protein truncation or single amino acid changes, and no genotype–phenotype correlations have so far become apparent. The biological function of *LGI1* has been extensively investigated in recent years, but to date no clear-cut picture has emerged. A first study established that *LGI1* was a novel subunit of the voltage-gated potassium (K_v) channel subunit $K_{v1.1}$ and suggested that *LGI1* mutations induce changes in the inactivation gating of presynaptic A-type channels [42]. Another study showed that LGI1 is a secreted protein that enhances AMPA receptor-mediated synaptic transmission through the binding of ADAM22, a transmembrane protein that when mutated itself causes seizure [43]. The presence of two different isoforms, one secreted and the other retained within the cell, may underlie the complex biological function of LGI; however, further studies will be necessary to clarify the role of *LGI1* in epileptogenesis [44]. As was observed in other mendelian epilepsies, a consistent proportion of families (about 50%) fulfilling the clinical criteria of ADPEAF do not show *LGI1* mutations [45]. The screening of *LGI1* is recommended in suggestive families for diagnosis confirmation. The prognostic value of the test is limited because of the variable clinical expressivity of *LGI1* mutations.

Benign familial adult myoclonic epilepsy

Benign familial adult myoclonic epilepsy (BFAME) is a rare phenotype characterized by tremulous finger movements and/or myoclonus of the extremities and rare generalized tonic–clonic seizures [46]. Myoclonus is easily precipitated by photic stimuli and sporadically by insomnia and fatigue. Peculiar electrophysiological findings are generalized spikes or poly-spikes and slow-wave complexes in the EEG, enlarged cortical components of somatosensory-evoked potential and enhanced long-loop C-reflex. No neurological degeneration, dementia or ataxia are found in BFAME patients, as have been observed for other mendelian idiopathic forms of epilepsy. Myoclonic jerks and tremulous finger movements typically begin around between adolescence and the third decade of life. Generalized tonic–clonic seizures manifest later with a sporadic occurrence [47]. This late age at onset is a distinctive sign of BFAME. Clonazepam or sodium valproate is usually effective in treating the disorder, though the tremulous finger movements may not disappear with therapy.

Family studies indicate that BFAME is an autosomal dominant trait showing high/complete penetrance and genetic heterogeneity. A BFAME gene has been localized on chromosome 8q24 [48,49] and chromosome 2p11.1–q12.2 [50,51]; since the mutant genes have not yet been identified, no genetic tests are available other than linkage analysis of chromosome 8q and 2p loci on informative extended pedigrees. The accurate analysis of clinical and electroclinical findings and the pattern of inheritance can yield critical clues to establishing a diagnosis and providing genetic counselling.

Despite considerable clinical and electroclinical diversity, the mendelian idiopathic forms of epilepsy so far described share important genetic features:

- Mendelian idiopathic forms segregate with autosomal dominant inheritance.
- Different genes are involved in the same phenotype, thus indicating genetic heterogeneity.
- Sporadic cases of mendelian forms are occasionally found, the significance of which is not fully understood. Possible explanations include failure to recognize familial clustering, *de novo* mutations arising from non-carrier individuals and inadequate differential diagnosis from other epileptic conditions.
- Genetic tests for mendelian idiopathic forms of epilepsy are not yet available or are very costly (e.g. mutational screening of different genes).

In light of the above considerations, genetic counselling in cases of mendelian epilepsy should rely on careful analysis of clinical signs in patients and family members and on recognition of a clear pattern of transmission. When available, genetic testing may be

undertaken to confirm the diagnosis and to better estimate recurrence risks in relatives of affected individuals.

Complex epilepsies

In human genetics, the term 'complex' refers to conditions arising from multiple concomitant factors of either genetic (polygenic inheritance) or genetic and environmental origin (multifactorial inheritance). In mendelian disorders, the mode of inheritance may be easily deduced from the analysis of transmission patterns within pedigrees. In complex disorders, segregation of the disease does not fit a precise pattern and more exhaustive epidemiological studies are needed in order to define the mode of inheritance. In genetic epidemiology, important indexes are defined in terms of the clinical concordance of monozygotic (MZ) twins and the risk of recurrence for different degree relatives of affected individuals. The first index indicates the heritability of a disorder; the second indicates the complexity of the genetic component. The higher the concordance rate among MZ twins, the stronger the contribution of genetic factors to the disorder. The higher the risk for relatives of probands, the fewer the genetic factors involved. Many forms of epilepsy show a complex inheritance, and epidemiological data are the only available tools for genetic counselling.

Idiopathic generalized epilepsies

The term idiopathic generalized epilepsies (IGEs) covers the most common forms of idiopathic epilepsy and includes childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic–clonic seizures only (EGTCS), as defined by the 1989 International Classification of Epileptic Syndromes and further modifications [5,6].

Several epidemiological studies have been conducted in recent decades in order to dissect the genetic aetiology of IGE. Although different methodological approaches have been adopted, results agree on a concordance rate of about 70–80% in MZ twins, increasing up to 90% when epileptiform EEG changes are considered [52–54], and a risk of developing IGE for first-degree relatives of probands of about 5–15% (compared with a cumulative incidence of about 0.5% in the general population) [55,56]. The recurrence risk for first-degree relatives is significantly lower in IGE than in single-gene disorders; when second-degree or more distant relatives are considered, the risk is close to that of the general population.

When considered together, the high concordance rate in MZ twins and the rapid decrease in risks for more distant relatives indicate a strong but complex genetic aetiology [57]. The involvement of multiple interacting susceptibility genes would result in low familial clustering and the absence of a recognizable pattern of inheritance. On the other hand, large and dense pedigrees are rarely found and suggest mendelian inheritance for a subset of IGE cases (Table 27.3).

The Rochester study has drawn up various clinical parameters in order to further refine recurrence risks for relatives of affected individuals [55,56].

- *Risk for siblings*. When all forms of epilepsy are considered, the risk of developing epilepsy for a sibling of a proband is about 4%. This increases to 6% when the IGE subgroup is considered and to 8% if photosensitivity is found in the proband or if a parent has epilepsy. The risk of developing generalized epilepsy for a sibling rises to 12% when a parent also shows generalized EEG abnormalities and to 15% when the sibling shows a generalized EEG trait.
- *Risk for offspring*. For all forms of epilepsy, the risk of recurrence for offspring of affected individuals is about 4–6%. A striking difference is seen between the offspring of affected females (8.7%) and those of affected males (2.5%) but it is not yet understood why. If the IGE subgroup is considered, the risk for offspring increases to about 9%.

Interestingly, if EEG abnormalities are considered, a recurrence rate of about 25–30% is found for specific traits (e.g. generalized spike–wave 3 Hz or generalized poly-spike EEGs) in first-degree relatives of probands [58,59]. Clinical variability among family members provides further epidemiological evidence. A study of 74 families with at least three members affected by IGE showed that only 25% of the families were concordant for a specific IGE syndrome, whereas 75% of families segregated at least two IGE

Table 27.3 Complex epilepsies.

Disease	Mode of inheritance and empiric risks for first-degree relatives	Rare mendelian subsets	Mode of inheritance	Gene(s)
Idiopathic generalized epilepsies (childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalized tonic–clonic seizures only)	Polygenic/multifactorial Risk for first-degree relatives: Seizures 5–15% Generalized spike-wave EEG trait 20–30%	Juvenile myoclonic epilepsy Childhood absence epilepsy with tonic–clonic seizures	AD (penetrance 0.7) AD (penetrance 0.8)	*EFHC1*, *GABRA1* *GABRB3*
Rolandic epilepsy	Polygenic/multifactorial Risk for first-degree relatives: Seizures: 10% Centrotemporal spikes: 20–30%	Rolandic epilepsy and speech dyspraxia Rolandic epilepsy and exercise-induced dystonia and writer's cramp	AD AR	 Unknown
Temporal lobe epilepsy	Sporadic conditions: no increased risk for relatives	Familial partial lobe epilepsy with variable foci Familial mesial temporal lobe epilepsy	AD AD (low penetrance)	Unknown Unknown

AD, autosomal dominant; AR, autosomal recessive.

syndromes [60]. These data reinforce the hypothesis that IGE might represent a clinical continuum which is determined by a cohort of susceptibility genes.

Efforts have been made to identify both susceptibility alleles for common forms of IGE and major genes involved in rare mendelian subsets. In various studies, putative susceptibility loci have been localized [61–63]. One such susceptibility allele for JME has been localized within the *BRD2* gene on chromosome 6p [64], but the role of *BRD2* in IGE is still controversial [65]. Thus, so far, there are no well-established genetic variations associated with genetic susceptibility to IGE and no tests available to estimate the risk. Mutations in rare autosomal dominant subsets have been identified for CAE (*GABRB3*) [66] and for JME (*GABRA1* and EFHC1) [67,68].

In clinical practice, the estimation of recurrence risks for relatives of individuals affected by IGE is, in most situations, based on epidemiological data. A possible methodological approach to the estimation of risks for IGE has been proposed above. The mutations identified in a few autosomal dominant pedigrees are rare and the implementation of any genetic test in the diagnostic workup is not recommended.

Idiopathic partial epilepsies

Different forms of partial epilepsy have been described, which have a complex genetic origin (Table 27.3).

Benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy)

Rolandic epilepsy is a common disorder characterized by brief, focal, hemifacial motor seizures that usually manifest during sleep and frequently evolve into generalized tonic–clonic seizures. The seizures typically begin between 3 and 13 years of age, and abate by the age of 16 years. The EEG hallmark of the syndrome is a striking age-dependent centrotemporal spike discharge. The spike discharge can occur in family members without the occurrence of seizures. The genetics of rolandic epilepsy are complex and controversial. Although the rate of clinical concordance in MZ twins has varied from 0% to 100% in different studies, it is widely accepted that genetic factors are involved in the aetiology of rolandic epilepsy [54,69,70]. A 15% risk of developing rolandic epilepsy has been reported for first-degree relatives of probands; this rises to about 30% if centrotemporal EEG abnormalities are considered [71]. In view of this, polygenic and multifactorial inheritance have each been proposed for seizures, and a pseudo-dominant mode of inheritance for rolandic discharges. So far, however, the mode of inheritance is unclear. Rolandic epilepsy has also been found to segregate in association with other neurological conditions, thus defining a few rare mendelian phenotypes such as the increasingly recognized condition named rolandic epilepsy and speech dyspraxia [72–74] or the autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp [75].

Familial temporal lobe epilepsy

Temporal lobe epilepsy is generally considered have a lesional origin (in other words to be a symptomatic epilepsy), although it has long been recognized that some cases have a positive family history [76,77]. In recent years, different familial forms of temporal epilepsy have been described. Most of these represent rare phenotypes observed in one or few pedigrees. Autosomal dominant temporal lobe epilepsy may be found in families with the *LGI1* mutations as a part of the ADPEAF phenotype [35–38, see above]. Temporal lobe epilepsy has, furthermore, been found to segregate in a condition known as familial partial epilepsy with variable foci (FPEVF) and a gene has been mapped on chromosome 22q [78]. In addition, the description of a few families with multiple members affected by mesial temporal lobe epilepsy indicates that genetic factors may exceptionally underlie this condition [79,80]. However, no pathogenic mutations have been identified so far and genetic testing is not available for the most common forms of temporal lobe epilepsy. The recognition of rare mendelian phenotypes through the analysis of specific clinical and familial data is critical to identifying high-risk pedigrees. On the other hand, the risk of developing a temporal lobe epilepsy for offspring or siblings of probands with negative family history is not significantly increased.

Sporadic epileptic syndromes

For some epilepsies, neither hereditary nor environmental or lesional causes have unequivocally been identified. Most of these are complex and usually severe phenotypes with onset in infancy or early childhood, such as West syndrome, Lennox–Gastaut syndrome, epilepsy with myoclonic–astatic seizures, and severe myoclonic epilepsy in infancy. The identification of mutations within the neuronal sodium channel gene *SCN1A* in severe myoclonic epilepsy in infancy (SMEI) patients yielded important insight into the genetics of severe sporadic epileptic conditions [81].

Severe myoclonic epilepsy in infancy

Severe myoclonic epilepsy in infancy manifests itself within the first year of life with tonic, clonic or tonic–clonic seizures. Seizures are frequent and prolonged and are often associated with fever. Later in life, patients develop atypical absence, myoclonic, generalized tonic–clonic and partial seizures. Psychomotor development is normal at onset but development stagnation and progressive ataxia occur after the second year. Seizures are usually refractory to drug therapy [82].

Although a positive familial history of febrile seizures has been described, SMEI manifests itself as a sporadic condition [83,84]. In at least 70% of patients, SMEI is due to *de novo* mutations in the neuronal sodium channel gene *SCN1A,* which occur during gametogenesis in one of the parents. Thus, the lack of familial clustering observed in SMEI is consistent with the sporadic occurrence of *SCN1A* mutations. From this standpoint, SMEI is a genetic disorder even though it is not usually hereditary. The occurrence of SMEI in siblings has been rarely reported and is attributed to the presence of a somatic or a germline mosaicism in one of the parents [85]. Interestingly, *SCN1A* is also involved in other severe related encephalopathies [86,87] and in GEFS^{+} syndrome [26, see above]. Genotype–phenotype correlations indicate that mutations resulting in the premature truncation of the channel subunit (e.g. nonsense, frameshift) lead to severe encephalopathic phenotypes whereas mutations affecting a single amino acid (e.g. missense) lead to either severe or milder epileptic trait according to the functional consequence on channel activity [88].

In addition, about 5% of the SMEI patients show a genomic deletion affecting part of the entire *SCN1A* gene [89]. The investigation of the epileptic *SCN1A* knockout mouse revealed a selective deficit of the voltage-gated sodium current in GABAergic neurones [90]. Thus, the observed differences in severity are probably due to the different effects of mutations on *SCN1A* function: in SMEI, channel activity is heavily impaired, whereas in GEFS$^+$ a residual activity is maintained. As more than 70% of the SMEI patients have mutations in the *SCN1A* gene, the screening of *SCN1A* is a valuable diagnostic tool [88]. The test has a significant clinical utility by allowing the early diagnosis with significant impact in the management of the patients. In addition, the identification of *SCN1A* mutations may assist the parents of a proband in planning future pregnancies. Indeed, the recurrence risk for parents with a child carrying a *de novo* mutation is low, except in the rare situation in which somatic or germline mosaicism occurs that may not be detectable by routine genetic testing.

Febrile seizures

The most common precipitant of seizures is fever and 3% of the population experience febrile seizures during childhood. Although febrile illnesses are acquired, pre-existing inherited factors determining a low threshold for febrile seizures are indicated by the high rate of familial clustering.

Febrile seizures have long been observed to occur in pedigrees. In MZ twins, clinical concordance has been found to be increased by 35% to 70%, depending on ascertainment strategy [91,92]. Epidemiological studies have reported an increased risk for first-degree relatives of probands, ranging from 8% in whites to up 20% in Japanese, in comparison with rates of 3% and 7% respectively in the general populations [93,94]. The mode of inheritance is by definition multifactorial, since an acquired condition is needed to trigger seizures. By contrast, the mode of transmission of genetic susceptibility is controversial. Polygenic inheritance has been proposed as most common, whereas pseudodominant inheritance has been suggested for rare large pedigrees [95]. A clinical approach has attempted to differentiate high-risk families segregating high-penetrant genes from the general population. Whether the number of seizures occurring in patients and EEG abnormalities correlate with higher recurrence risk is controversial.

A major epidemiological finding is the 2- to 10-fold increased risk for febrile seizures probands of developing afebrile seizures later in life. On the basis of retrospective studies, it has been proposed that prolonged febrile seizures frequently observed in the history of patients with temporal lobe epilepsy may lead to mesial temporal sclerosis [96,97]. On the other hand, genetic factors underlying febrile seizures could also confer liability to epilepsy [29].

Recent studies have provided clues to the mode of inheritance of febrile seizures and their relationship with epilepsy. Genotype–phenotype correlations in GEFS$^+$ families demonstrate that about 90% of individuals carrying mutations on *SCN1A*, *SCN1B* and *GABRG2* genes show febrile seizures and about half of these develop idiopathic generalized epilepsy [26–28]. Thus, early epidemiological data indicating autosomal dominant inheritance in a subset of febrile seizures cases and a common genetic aetiology for febrile seizures and epilepsy found strong support from biological evidence. On the other hand, the lack of causative genes for pure febrile seizures provides an indirect confirmation of this genetic complexity.

Genetic counselling in febrile seizures relies on empirical epidemiological data. The recognition of occasional autosomal dominant subsets of febrile seizures (including GEFS$^+$ syndrome) that may manifest as non-specific familial clustering of febrile seizures cases should, however, lead to caution when attempting to identify high-risk subjects.

Genetic syndromes including epilepsy as an important clinical feature

A variety of genetic syndromes include epilepsy as an important component (Table 27.4). The seizure disorders in these conditions usually consist of symptomatic generalized epilepsies associated with structural brain lesions and/or metabolic abnormalities of

Table 27.4 Genetic syndromes including epilepsy as important feature.

Group	Name of disease
Neurocutaneous	Tuberous sclerosis
	Neurofibromatosis
Malformations of cortical development	Ito hypomelanosis
	Miller–Dieker syndrome
	X-linked lyssencephaly
	Subcortical band heterotopia
	Polymicrogyria
	Periventricular nodular heterotopia
Neurological	Dentatorubropallidoluysian atrophy
	Fragile X syndrome
	Angelman's syndrome
	Down syndrome (tri 21)
	Wolf–Hirschhorn (4p–)
	Ring chromosome 20
	Huntington's disease
Metabolic	Rett's syndrome
	Progressive myoclonic epilepsies (PMEs)
	Alpers' disease
	Non-ketotic hyperglycinaemia
	D-Glyceric acidaemia
	Proprionic acidaemia
	Sulphite oxidase deficiency
	Fructose 1,6-diphosphatase deficiency
	Piridoxine dependency
	Aminoacidopathies
	Urea cycle disorders
	Disorders of carbohydrate metabolism
	Disorders of biotin and folic acid metabolism
	Glucose transport protein deficiency
	Menkes' disease
	Glycogen storage disorders
	Krabbe's disease
	Fumarase deficiency
	Peroxisomal disorders
	Sanfilippo's syndrome
	Mitochondrial encephalopathy, lactic acidosis and stroke-like (MELAS) syndrome
	Pyruvate dehydrogenase deficiency
	Respiratory chain defects

genetic origin. Malformational, metabolic, neurocutaneous and tumorous disorders showing chromosomal, single-gene and complex inheritance are included. Among these, progressive myoclonus epilepsies deserve special discussion.

Progressive myoclonus epilepsies

Progressive myoclonus epilepsies (PME) are a group of disorders characterized by myoclonic seizures, tonic–clonic seizures and progressive neurological dysfunction, in particular ataxia and dementia. Myoclonus is quite severe, with bilateral synchronous or multifocal asyncronous manifestations often affecting facial and bulbar muscles in addition to limbs. Convulsive seizures and neurological decline may predominate over myoclinic manifestations in some patients. Amongst the commonest causes of PME are Unverricht–Lundborg disease, Lafora's disease, myoclonus epilepsy and ragged red fibres (MERRF), sialidoses and neuronal ceroid lipofuscinoses. Although these conditions show substantial overlapping with other progressive encephalopathies (e.g. GM2 gangliosidosis) or progressive myoclonic ataxias (e.g. spinocerebellar ataxias), the strong contribution of the epileptic manifestations to the phenotype has led PMEs to be classified into epileptic disorders [5]. Autosomal recessive inheritance is always found, except in MERRF, which is maternally transmitted through mitochondrial DNA (Table 27.5).

Unverricht–Lundborg disease

Initially described in Finland, Unverricht–Lundborg disease is a rare disorder subsequently recognized worldwide, the clinical features of which include an onset at age 8–13 with myoclonus or tonic–clonic seizures, mild progression to ataxia and dementia, and neuronal loss with no evidence of storage material [98]. Some individuals show slow disease progression and others a faster course, even within the same family, and in many patients the condition deteriorates slowly and then the disability becomes static. Improvement may be obtained with sodium valproate, whereas phenytoin is deleterious [99].

The mutation causing Unverricht–Lundborg disease affects the gene encoding cystatin B (CSTB), which is involved in the inhibition of a group of lysosomal proteases known as cathepsins [100]. The most common mutation is an expansion of an unstable dodecamer repeat in the 5′-untranslated region, which suppresses transcription. In the general population, two or three repeats usually occur, whereas up to a hundred repeats are found in patients. However, no correlation between clinical severity or age at onset and size of expansion has been observed [101]. Alleles in the range of 12–17 repeats have been found to be unstably transmitted to offspring. These alleles are not associated with clinical phenotypes and are therefore called 'premutational'. Most patients are homozygous for dodecamer expansion; point mutations are occasionally found in compound heterozygous patients.

Identification of the clinical features is the first step in diagnosing the disease. When suggestive indications are found, mutational analysis of CSTB may be attempted. Genetic testing is also a powerful tool for prenatal diagnosis and for the identification of carriers among at-risk individuals.

Lafora's disease

Lafora's disease is a rare disorder with onset between the ages of 10 and 18 years, characterized by progression to inexorable dementia and frequent occipital seizures, in addition to myoclonus and

Table 27.5 Progressive myoclonus epilepsies.

Disease		Age at onset	Suggestive clinical features	Suggestive laboratory features	Genetics	Gene(s)
Unverricht–Lundborg disease		8–13 years	Severe myoclonus, mild dementia and ataxia	None identified	AR	*CSTB*
Lafora's disease		10–18 years	Severe myoclonus, occipital seizures, inexorable dementia, Lafora bodies	Lafora bodies in skin biopsies	AR	*EPM2A* *EPM2B*
Myoclonus epilepsy and ragged red fibres (MERRF)		Variable	Deafness, optic atrophy, myopathy, myoclonus	Ragged red fibres, increased level of pyruvate and lactate (blood)	Mitochondrial	$tRNA^{lys}$
Sialidoses	Type I	8–20 years	Severe myoclonus, tonic–clonic seizures, ataxia, cherry-red spot, visual failure	Elevated urinary sialyloligosaccharides, deficiency of neuroaminidase in leucocytes and cultured skin fibroblasts	AR	*NEU*
	Type II	10–30 years	Severe myoclonus, ataxia, cherry-red spot, visual failure, dysmorphic features, hearing loss	Elevated urinary sialyloligosaccharides, deficiency of neuroaminidase and β-galactosidase in leucocytes and cultured skin fibroblasts	AR	*PPGB*
Neuronal ceroid lipofuscinoses	CLN2	2.4–4 years	Myoclonic, tonic–clonic, atonic or atypical absence seizures, psychomotor delay and ataxia, visual failure	Curvilinear, rectilinear or fingerprint lipidic inclusions in skin biopsy at electron microscopy	AR	*TPP1*
	CNL3	5–10 years	Myoclonus and tonic–clonic seizures, macular degeneration, optic atrophy, dementia		AR	*CLN3*
	CNL4	15–50 years	Generalized seizures, myoclonic jerks, extrapyramidal symptoms		AR/AD	–

AD, autosomal dominant; AR, autosomal recessive.

tonic–clonic seizures. Prognosis is poor, with death occurring 2–10 years after onset [102]. A distinctive feature of the disease is the occurrence of polyglucosan inclusions (Lafora bodies) in neurones and in various other tissues [103]. In 1998 the gene involved in Lafora's disease (*EPM2A*) was identified as the gene encoding dual-specificity phosphatase (laforin) [104], a cytoplasmic protein associated with polyribosomes and possibly involved in the translational regulation of glycogen metabolism. Microdeletions and point mutations are observed in all four exons, although R241X is found in about 40% of patients [105]. In a proportion of patients with typical Lafora's disease that varies considerably between populations, the disorder is due to mutations in a second gene with unknown function called *EPM2B* [106]. *EPM2B* mutations include point mutations as well as deletions affecting the entire gene. The pathogenic mechanisms leading to polyglucosan accumulation in Lafora bodies have not yet been clearly elucidated and alternative models have been proposed which involve up-regulation of glycogen synthase activity [107] or suppression of glycogen phosphorylation, an essential process of normally structured glycogen [108]. Clinical diagnosis is not usually difficult when the disease is fully developed. Lafora bodies detected in skin biopsies constitute a unique marker. Pathological examination, however, is laborious and may lead to either false-positive or false-negative results. Conversely, genetic testing based on mutational screening of *EPM2A* and *EPM2B* shows a very high sensitivity and has become the preferred diagnostic tool. Genetic testing is of critical importance for prenatal diagnosis and carrier identification.

Myoclonus epilepsy and ragged red fibres

Myoclonus epilepsy and ragged red fibres is a mitochondrial disorder characterized by a broad clinical spectrum and intrafamilial variability in severity and age of onset. In addition to typical PME manifestations, patients may show deafness, optic atrophy and myopathy [109]. The pathological changes and other findings such as decreased metabolism for glucose and oxygen on positron emission tomography (PET) and an increase in organic phosphate in resting muscle indicate a possible dysfunction in the mitochondrial respiratory chain. However, biochemical assays of mitochondrial respiratory enzymes may be normal and ragged red fibres absent, suggesting a complex pathogenesis [110].

Myoclonus epilepsy and ragged red fibres is inherited through the maternal line as a paradigmatic example of mitochondrial inheritance. Clinical variability is dependent on the amount of mutated mtDNA. In this perspective, MERRF may also manifest as a sporadic condition. A missense mutation (*A8344G*) affecting the $tRNA^{lys}$ and, consequently, the translation of all genes encoded by the mtDNA has been described [111].

Although increased levels of pyruvate, lactate and ragged red fibres are often found, identification of clinical signs is crucial for diagnosis. In the presence of suggestive clinical data, the analysis of *A8344G* mutations is an excellent diagnostic tool. Genetic testing may also be used to perform prenatal diagnosis and to identify at-risk individuals.

Sialidoses

The sialidoses are very rare autosomal recessive lysosomal disorders characterized by complex phenotypes subgrouped into sialidosis type I and type II.

Occurring in the second decade of life, sialidosis type I presents with cherry-red macular spots, progressive severe myoclonus, gradual visual impairment, tonic–clonic seizures and ataxia without dementia [112]. Sialidosis type II includes complex phenotypes showing additional clinical symptoms such as coarse facies, corneal clouding, mental impairment and hearing loss, and may be subdivided into juvenile and infantile forms depending on the age of onset [113].

Neuronal lipidosis and vacuolated Kupffer cells are distinctive histological findings in sialidoses. Clinical diagnosis can be confirmed by documenting elevated urinary sialylyl-oligosaccharides and a deficiency of α-*N*-acetylneuroaminidase in leucocytes and cultured skin fibroblasts [113]. In some cases of type II sialidosis – predominantly in Japanese cases of juvenile type II sialidosis – β-galactosidase deficiency is found in addition to neuroaminidase deficiency [113]. Complementation between neuroaminidase-deficient cells and combined neuroaminidase/β-galactosidase deficiency suggests different genetic aetiology and pathogenesis [114]. Thus, classification of sialidoses into type I and II has only a clinical value, whereas the definition of neuroaminidase deficiency and galactosialidosis best describes the aetiology and pathogenesis of sialidoses.

Mutations in the neuroaminidase gene (*NEU*) on chromosome 6p have been detected in neuroaminidase deficiency [115]. In galactosialidosis, mutations were found within the cathepsin A gene on chromosome 20q encoding a 32-kDa protein (PPGB, protective protein for beta-galactosidase), which is required to protect galactosidase from degradation and to promote the catalytic action of neuroaminidase [116]. Genotype–phenotype correlations in neuroaminidase deficiency indicate that type I or type II sialidosis occurs depending on the residual activity of neuroaminidase resulting from different mutations.

Biochemical assays focus on measuring the activity levels of neuroaminidase and β-galactosidase. Mutational screening of the NEU and PPGB genes is a powerful tool for confirming the clinical diagnosis in probands and can be utilized in prenatal diagnosis and carrier identification.

Neuronal ceroid lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs) are autosomal recessive neurodegenerative disorders characterized by accumulation of ceroid lipopigment of granular, curvilinear or fingerprint appearance in the lysosomes of various tissues. According to the age of onset and clinical variants, various NCLs have been described over the years, leading to a complex classification comprising at least seven different forms [117]. Among these, CLN2, CLN3 and CLN4 are most commonly involved in PME, whereas infantile neuronal ceroid lipofuscinosis (CLN1) does not manifest as PME. CLN5, CLN6 and CLN8 are very rare disorders restricted to specific geographical areas.

Neuronal ceroid lipofuscinosis, late infantile type (CLN2)

Late infantile NCL displays myoclonic, tonic–clonic, atonic or atypical absence seizures between 2.5 and 4 years of age. Psychomotor delay and ataxia appear a few months later, whereas visual failure develops as the disease progresses. Prognosis is very poor, in that seizures are intractable, dementia is relentless and death usually occurs by the age of 5 years [118]. The gene has been

localized on chromosome 11 and identified as encoding tripeptidyl peptidase 1 (TPP1) [119]. Although affected individuals are sometimes clustered in specific areas (e.g. Newfoundland), cases have been reported worldwide and several different mutations reported.

In the past, electron microscopy detection of typical curvilinear lipidic inclusions was used to confirm the clinical diagnosis and to reach a prenatal diagnosis in uncultured amniocytes. The recent cloning of the gene has provided a further tool for the diagnosis of late infantile NCL.

Neuronal ceroid lipofuscinosis, juvenile type or Batten's disease (CLN3)

This disease usually appears between 5 and 10 years of age, with rapid deterioration of vision and progressive dementia. Macular degeneration, optic atrophy and attenuated vessels are revealed by fundoscopy. Seizures may be minor manifestations or major symptoms involving myoclonus and tonic–clonic seizures. Although the clinical course may vary among patients, death usually occurs within about 10–12 years of onset [120]. The Batten's disease gene encodes for an integral membrane protein (CLN3) that is primarily localized in the Golgi apparatus. More than 20 different mutations have been observed so far [121]. However, a 1-kb deletion is found in 70% of disease chromosomes, suggesting a strong founder effect.

Diagnosis may be established by electron microscopy examination of curvilinear and rectilinear bodies and fingerprint profiles in skin biopsies. The presence of inclusions in heterozygous carriers is controversial. Mutational screening of *CLN3* may also be attempted for the molecular diagnosis of Batten's disease.

Neuronal ceroid lipofuscinosis, adult type (Kufs' disease)

Kufs' disease is a very rare disorder characterized by generalized seizures with onset around 30 years of age and a subsequent cerebellar syndrome presenting with myoclonic jerks and extrapyramidal symptoms. Notably, fundoscopy examination is normal and blindness is absent. Death occurs within about 10–12 years of onset [122]. The pattern of inheritance is still unclear, in that both autosomal dominant and autosomal recessive inheritance have been described [123,124]. Since the Kufs' disease gene has not yet been localized or cloned, electron microscopy examination of muscle biopsies to detect curvilinear bodies is the only diagnostic test available.

Conclusion

Epilepsy is a complex phenotype with a complex aetiology. A variety of syndromes differing in clinical and physiological manifestations, pharmacological properties and prognosis are influenced by multiple factors of acquired and genetic origin. Genetic aetiology is highly heterogeneous and autosomal dominant, autosomal recessive, polygenic, mitochondrial and multifactorial disorders are found. Genetic counselling in epilepsy therefore has to deal with a composite picture in which recurrent seizures may be the expression of individually acquired conditions and/or familial background. The genetics of several hereditary forms of epilepsy are still poorly understood and genetic counselling frequently has to rely on empirical data alone, as in the case of idiopathic generalized epilepsy, rolandic epilepsy or febrile seizures.

Table 27.6 Genetic testing in epilepsy.

Disorder	Gene(s)	Diagnostic validity	Clinical utility
Benign familial neonatal seizures	*KCNQ2* *KCNQ3*	High in correct clinical context	Limited – *KCNQ2/KCNQ3* mutational analysis does not alter management or prognostic implications
Benign familial neonatal–infantile seizures	*SCN2A*	High in correct clinical context	Limited – *SCN2A* mutational analysis does not alter management or prognostic implications
Generalized epilepsy with febrile seizures plus	*SCN1A, SCN1B, GABRG2*	High in correct clinical context	No – variable expressivity of mutations. Mutation does not inform about prognosis or treatment
Severe myoclonic epilepsy of infancy (SMEI)	*SCN1A*	High in correct clinical context	Yes – early optimization of antiepileptic therapy. Implications for genetic counselling
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4, CHRNB2, CHRNA2*	High in correct clinical context	Yes – establish aetiology, no need of follow-up imaging. Implications for genetic counselling
Autosomal dominant partial epilepsy with auditory features	*LGI1*	High in correct clinical context	Yes – establish aetiology, no need of follow-up imaging. Implications for genetic counselling
Unverricht–Lundborg disease	*CSTB*	High	Yes – inform about prognosis and treatment. Implications for genetic counselling. Detection of at-risk individual
Lafora's disease	*EPM2A* *EPM2B*	High	Yes – inform about phenotype, prognosis and treatment. Implications for genetic counselling. Detection of at-risk individual
Myoclonus epilepsy and ragged red fibres (MERRF)	$tRNA^{lys}$	High	Yes – variable expressivity of mutations. Mutation does not inform about prognosis or treatment. Implications for genetic counselling. Detection of at-risk family members
Sialidoses	*NEU* *PPGB*	High	Yes – inform about prognosis. Implications for genetic counselling. Detection of at-risk family members
Late infantile neuronal ceroid lipofuscinoses	*TPP1*	High	Yes – inform about prognosis. Implications for genetic counselling. Detection of at-risk family members
Juvenile neuronal ceroid lipofuscinoses	*CLN3*		Yes – inform about prognosis. Implications for genetic counselling. Detection of at-risk family members

We should, however, be aware of the significant advances that have been made in recent times. The genetic mechanisms of most inherited conditions underlying severe epileptic phenotypes such as progressive myoclonus epilepsies have been successfully investigated. Genetic tests for the identification of at-risk carriers and for prenatal diagnosis are being developed and more accurate estimates of recurrence risks can be provided (Table 27.6).

In idiopathic forms of epilepsy, different genes have been linked to mendelian phenotypes, and neuronal ion channels are promising candidates for investigating pathogenetic processes. The presence of many ion-channel genes in the genome provides a promising working hypothesis for many idiopathic epileptic disorders of unknown genetic aetiology. A paradigmatic example is *SCN1A*, which was initially associated with the GEFS$^+$ phenotype and was subsequently found to be mutated in severe myoclonic epilepsy of infancy. Mendelian subsets have also played an important role in proving genetic aetiology in apparently symptomatic forms of epilepsy such as temporal lobe epilepsy.

It will probably take a long time to dissect the complex aetiology of hereditary forms of epilepsy and before clinical practice and genetic counselling gain significant benefits. There is no doubt, however, that the journey has already begun.

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28 Drug Interactions

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Introduction

The widespread use of co-medications in current medical practice carries the risk of drug interactions. While certain drug combinations may be used advantageously, in many cases multiple drug therapy reduces the therapeutic efficacy or increases the toxicity of one or more of the administered compounds.

Drug interactions are a frequent complication in patients treated with antiepileptic drugs (AEDs) for a variety of reasons [1,2]. The AEDs are usually administered for prolonged periods, often for a lifetime, increasing the probability of co-medication. They are often prescribed in combination with other AEDs or medications used for the management of associated disorders. Approximately 70% of patients with epilepsy can be made seizure free by currently available AEDs given as monotherapy. In most of the remaining patients, better control can be achieved only with long-term AED polytherapy. All newer AEDs are given as a first prescription as add-on therapy in patients with chronic refractory partial epilepsy, so polytherapy will initially be the only option for these agents. In addition, AEDs are widely used to treat other non-epilepsy disorders such as bipolar disorder, migraine and chronic pain, further enhancing the possibility of combination therapy. Their pharmacokinetic properties also make the AEDs particularly susceptible to drug interactions. Many of the older AEDs have a narrow therapeutic index, and even a relatively small change in their plasma concentrations can easily result in loss of efficacy or signs of intoxication. Finally, some AEDs have prominent inhibitory or inducing effects on the activity of the hepatic enzymes which metabolize the majority of existing medications, while most of the old and new generation AEDs are substrates of the same enzyme systems. Compared with older agents, new AEDs appear to have clear advantages in terms of a lower potential for interaction [3–5].

The purpose of this chapter is to highlight the basic principles and mechanisms of drug interactions involving AEDs, providing necessary information to prevent or minimize their occurrence. Examples of specific clinically important interactions will be presented.

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Definition and basic types of drug interactions

A drug interaction can be defined as a quantitative or qualitative modification of a drug effect caused by concomitant administration of another drug [2]. In a broad sense, the responsible agent can be not only a drug but also a dietary component, a nutritional supplement, a herb, alcohol, tobacco or an environmental agent. The consequences of a drug interaction can be either beneficial, if the interaction results in increased therapeutic efficacy or reduced risk of adverse effects, or harmful, if it leads to decreased efficacy or enhanced toxicity of one or more of the administered compounds. Drug interactions may be clinically important not only when additional drugs are co-administered, but also when one or more drugs are discontinued. When an interacting drug is removed from a multidrug regimen, interaction processes go into reverse, possibly resulting in either reduced efficacy or increased risk of undesirable effects.

There are two basic types of drug interactions: pharmacokinetic and pharmacodynamic [2]. Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism or excretion of a drug and/or its metabolite(s) after the addition of another chemical agent. These interactions are associated with a modification in plasma concentration of either the drug or its metabolite(s) and alter the concentration of the active drug at the site of action. They account for most of the interactions reported to date as they are easily detected by a change in plasma drug concentrations. Pharmacodynamic interactions occur when two drugs act at the same or inter-related receptor sites, resulting in additive, synergistic or antagonistic effects. Pharmacodynamic interactions are less well recognized and are commonly inferred to explain drug-induced modifications in clinical status that cannot be ascribed to a pharmacokinetic mechanism. While this classification is useful for didactic purposes, it should be pointed out that many interactions involve a complex sequence of events at both pharmacokinetic and pharmacodynamic levels.

Pharmacokinetic interactions

Pharmacokinetic interactions may occur at the level of drug absorption, distribution, metabolism and excretion. The vast majority of pharmacokinetic interactions with AEDs arise as a consequence of drug-induced changes in hepatic metabolism, through enzyme inhibition or induction, and less frequently from changes in plasma protein binding [6]. In recent years, however,

the increasing recognition of the role played by drug transporters, notably P-glycoprotein, in the absorption, distribution and excretion of a wide variety of drugs has raised the possibility that other mechanisms may occasionally be involved [7]. P-glycoprotein is a multidrug efflux transporter, encoded by the *MDR1* gene (or *ABCB1*), highly expressed in the intestine, brain, liver and kidney, which acts as a natural defence mechanism against several substrates by limiting their absorption from the gut and penetration to the brain and promoting their elimination in the bile and urine [7].

Absorption

Absorption is the entry of a drug into systemic circulation via the mucous membranes of the guts or the lungs, via the skin or from the site of an injection. Oral intake is by far the most common route of administration of drugs including AEDs. Clinically significant drug interactions with AEDs are rare during absorption. In this respect, co-administration of antacids containing magnesium hydroxide or aluminium hydroxide has been reported to cause a moderate decrease in the absorption of phenytoin and gabapentin, presumably by decreasing the acidity of the stomach and also by the formation of insoluble complexes, thereby resulting in diminished plasma concentrations and, possibly, reduced efficacy [2]. Another example is the impaired absorption of phenytoin when given concurrently to epileptic patients receiving continuous nasogastric feeds, an effect that has been attributed to binding of phenytoin to constituents of the feeding formulas to form insoluble, not absorbable, complexes [3].

Drug transporters, notably P-glycoprotein, play an important role in the gastrointestinal absorption of many drugs [7]. The distribution of P-glycoprotein varies substantially across the gastrointestinal tract, and its role and contribution to drug absorption differs between drugs. At present, its role in the gastrointestinal absorption of AEDs is not fully understood. Within the intestinal epithelium, P-glycoprotein is found in close proximity to cytochrome P450 enzyme (CYP) 3A4. There is evidence that P-glycoprotein and CYP3A4 are an integral part of an intestinal defence system to protect the body against xenobiotics, and can be major determinants of bioavailability of orally administered drugs. Furthermore, most but not all substrates of CYP3A4 are also substrates of P-glycoprotein and inhibitors and inducers of CYP3A4 are usually also inhibitors and inducers of P-glycoprotein [8]. This interplay between transporters and drug-metabolizing enzymes makes it difficult to define transporter-mediated drug interactions [9]. It is likely that some AED interactions currently attributed to enzyme induction are in fact mediated by reduced gastrointestinal absorption or enhanced renal elimination – an example is the interaction in healthy subjects between carbamazepine and the β_1-blocker talinolol [10]. More recently, inhibition of the intestinal transporter for valproic acid absorption has been hypothesized as one of the mechanisms to explain the pronounced fall in plasma levels of valproic acid caused by concomitant administration of carbapenem antibiotics [11].

Distribution

Once a drug enters into systemic circulation, it is distributed in interstitial and intracellular fluids. Drugs are found in plasma either bound to serum protein or free (unbound). The principal proteins involved are albumin and α_1-acid glycoprotein. Generally, acid drugs bind predominantly to albumin, but not necessarily to the same site, while basic and neutral drugs bind to various sites on α_1-acid glycoprotein in addition to albumin. Plasma protein binding interactions can be due to competition between two drugs for binding sites on plasma proteins [3]. Displacement from plasma proteins will then cause a rise in the fraction of unbound drug in plasma or tissue, thereby potentially increasing the effect of the displaced drug. If the displacing drug is withdrawn, the reverse will occur. However, such interactions are likely to be clinically significant only if two criteria are fulfilled: (1) the displaced drug must be highly protein bound (usually greater than 90%) and (2) the drug must have a low volume of distribution. In fact, if the displaced drug is not highly bound, the amount displaced (which is usually of the order of a few per cent) will make little impact on the circulating unbound concentration, and if it is widely distributed to the tissues, any increase in the free concentration will be diluted by further distribution. Important drugs which fulfil these criteria and may therefore be object drugs in protein binding displacement interactions include warfarin, phenytoin and tolbutamide. The most common displacers from protein binding sites include sulphonamides, salicylates, chloral hydrate and some of its congeners (because of their metabolite trichloracetic acid), phenylbutazone and valproic acid.

The relevance of protein binding displacement interactions has been overestimated and such interactions are usually of no clinical significance [12,13]. For highly protein-bound drugs eliminated by low-extraction hepatic metabolism, such as phenytoin, the initial displacement may result in transient increase in free (or pharmacologically active) drug concentrations. However, the increased unbound drug is metabolized by the hepatic enzymes and a new steady state may occur. This new steady state results in a higher percentage of unbound drug but a lower total drug concentration, and therefore no overall change in the unbound plasma concentrations of the displaced drug [14,15]. In this situation, the monitoring of free rather than total drug concentrations can be more clinically useful, but in practice is seldom required.

Amongst AEDs, only valproic acid, phenytoin and tiagabine are highly bound to plasma proteins and liable to be displaced from protein binding sites [1,3]. The most common of these interactions is the displacement of phenytoin by valproic acid [3,16]. The effect of valproic acid on phenytoin pharmacokinetics is complex, being a combination of a protein binding displacement and enzyme inhibition. Valproic acid displaces phenytoin from plasma proteins, increasing its unbound fraction, and inhibits phenytoin metabolism, reducing its intrinsic clearance. Total phenytoin concentrations may be reduced, unchanged or occasionally even increased, but the concentration of free phenytoin is usually increased. As a result of this interaction, in patients co-medicated with valproic acid, therapeutic and toxic effects occur at total plasma phenytoin concentrations lower than usual. Valproic acid may also displace carbamazepine from plasma binding sites, but the magnitude of this interaction is generally small and without clinical significance.

Distribution of AEDs from the blood to the brain is necessary for a successful therapeutic outcome. There is conflicting evidence that P-glycoprotein plays a role in mediating the efflux of some

AEDs including carbamazepine, phenytoin, phenobarbital, lamotrigine and felbamate across the blood–brain barrier [3]. Therefore, the overexpression of P-glycoprotein in brain tissue could theoretically limit the penetration of AEDs to their sites of action and could be a potential mechanism of pharmacoresistance in epilepsy [17]. Moreover, it is possible that AED interactions are due to competition for transport across the blood–brain barrier via P-glycoprotein mechanisms.

Metabolism

The majority of clinically relevant pharmacokinetic interactions of AEDs occur at the level of drug metabolism. Metabolic processes are necessary to convert a non-polar (lipid-soluble) drug into one or more polar (water-soluble) metabolites, facilitating their excretion in urine or bile. Although metabolism usually results in inactivation or detoxification, many drug metabolites have pharmacological activity similar to or different from that of the parent molecule, and may therefore contribute to therapeutic outcome or be responsible for toxic effects. When metabolites are active, termination of their action occurs by further biotransformation or by direct excretion of the metabolite in urine or bile. The chemical reactions involved in the biotransformation of drugs are catalysed by various enzyme systems and can be classified as either phase I (functionalization) or phase II (conjugation) biotransformation reactions, which may occur in series. Phase I reactions involve the addition of a polar functional group (e.g. a hydroxyl group) or the deletion of a non-polar alkyl group (e.g. N-demethylation) by oxidation, reduction or hydrolysis. Phase II conjugation reactions lead to the formation of a covalent linkage between the drug or the phase I metabolite and a water-soluble endogenous substrate (e.g. glucuronic acid, acetic acid, sulphate, amino acids or glutathione), usually resulting in an inactive, easily excretable compound. The liver is usually the main organ responsible for phase I and phase II reactions, but other organs such as the gastrointestinal tract, the kidney, the lungs, the brain, the blood, the skin and the placenta may also contribute to metabolism. In the hepatocyte, phase I oxidative enzymes are located almost exclusively in the smooth endoplasmic reticulum, along with the phase II enzyme, glucuronyltranferase. Other phase II enzymes responsible for conjugation reactions are found predominantly in the cytoplasm.

Major enzyme systems involved in the metabolism of antiepileptic drugs

Knowledge of the major enzyme systems involved in the biotransformation of AEDs is essential for understanding the principles and mechanisms of metabolically based drug interactions.

Cytochrome P450 system

The human cytochrome P450 (CYP) system consists of a superfamily of more than 50 haem-containing enzymes, located in the membranes of the smooth endoplasmic reticulum in the liver and in many extrahepatic tissues, that are responsible for the phase I oxidative reactions of many drugs, nutrients, environmental toxins and endogenous substances [18]. These enzymes are categorized into families and subfamilies according to similarities in their amino acid sequence, with each enzyme being designated as CYP followed by a number indicating the family, a letter indicating the subfamily, and another number denoting the specific isoform [19].

The CYP isoenzymes playing a major role in the biotransformation of therapeutic agents are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Minor but clinically relevant isoforms include CYP2A6, CYP2B6, CYP2C8 and CYP2E1. Each CYP isoform is a specific gene product and possesses a characteristic but relatively broad spectrum of substrate specificity. Different CYP isoforms may display overlapping substrate specificities, that is one CYP isoenzyme can metabolize multiple substrates and most substrates can be metabolized by various CYP isoenzymes. There is a large variability in the expression and activity of these isoenzymes, which can lead to interindividual differences in drug metabolism. Such variability results from genetic, pathophysiological and environmental factors, including concomitant administration of other drugs. Mutations or polymorphisms in genes coding for CYP isoforms can result in enzyme variants with higher, lower or no activity, or occasionally the total absence of the enzyme. When a variant allele occurs in 1% or more of the population, it is referred to as genetic polymorphism [20]. The CYP polymorphisms that have the greatest clinical implications involve CYP2C9, CYP2C19 and CYP2D6. In recent years, the major CYP isoenzymes have been characterized at the molecular level and their different substrates, inhibitors and inducers have been identified (Table 28.1) [21,22]. As shown in Table 28.1, the majority of commonly used AEDs are metabolized by CYP enzymes and some of these may also act as inhibitors or inducers of one or more of these isoforms. The major CYP isoforms are described in more detail below [22–24].

CYP1A2

CYP1A2 accounts for approximately 10–15% of total hepatic CYPs and is the primary enzyme involved in the oxidative metabolism of many drugs, including theophylline, caffeine, tacrine, propranolol, mirtazapine, clozapine and olanzapine. With regard to AEDs, CYP1A2 contributes, to a minor extent, to carbamazepine metabolism. There is a wide interindividual variability in CYP1A2 activity, but the impact of genetic polymorphism on CYP1A2 metabolic capacity is controversial. The antidepressant fluvoxamine and various fluoroquinolone antibiotics (i.e. ciprofloxacin) are potent, but not selective, inhibitors of CYP1A2. The activity of CYP1A2 is induced by polycyclic aromatic hydrocarbons (including those found in charcoal-broiled foods and cigarette smoke), rifampicin, omeprazole and, possibly, by phenobarbital, phenytoin and carbamazepine.

CYP2C9

CYP2C9, the most abundant among human CYP2C isoforms, plays an important role in the oxidation of many drugs, including phenytoin, phenobarbital, S-warfarin (the active isomer of racemic warfarin), tolbutamide, losartan, fluvastatin and many non-steroidal anti-inflammatory agents such as diclofenac, ibuprofen, naproxen and piroxicam. CYP2C9 is polymorphically expressed in humans. To date, three different allelic variants that code for enzymes with different catalytic activity have been identified. The frequencies of the defective alleles CYP2C9*2 and CYP2C9*3 vary between 8% and 12% and 3% and 8% respectively among whites, but they are somewhat lower in Orientals and black

Table 28.1 Substrates, inhibitors and inducers of the major drug-metabolizing cytochrome P450 isoenzymes.

Enzymes	Substrates	Inhibitors	Inducers
CYP1A2	Antidepressants: amitriptyline, clomipramine, imipramine, fluvoxamine, mirtazepine, duloxetine Antipsychotics: haloperidol, clozapine, olanzapine Methylxanthines: theophylline, caffeine Miscellaneous: phenacetin, paracetamol, tacrine, tamoxiphen, *R*-warfarin	Ciprofloxacin Enoxacin Fluvoxamine Clarithromycin	Smoking Rifampicin Barbiturates Phenytoin Carbamazepine
CYP2C9	AEDs: phenytoin, phenobarbital, valproic acid NSAIDs: diclofenac, ibuprofen, naproxen, piroxicam, celecoxib Miscellaneous: *S*-warfarin, tolbutamide, losartan, torasemide, fluvastatin	Sulphaphenazole Amiodarone Fluconazole Miconazole Valproic acid Fluoxetine Fluvoxamine	Rifampicin Barbiturates Phenytoin Carbamazepine
CYP2C19	AEDs: phenobarbital, phenytoin, diazepam Antidepressants: amitriptyline, clomipramine, imipramine, citalopram, escitalopram Miscellaneous: diazepam, lansoprazole, omeprazole, propranolol, proguanil, *R*-warfarin	Omeprazole Ticlopidine Fluvoxamine Felbamate Topiramate (weak) Oxcarbazepine (weak)	Rifampicin Barbiturates Phenytoin Carbamazepine
CYP2D6	Antidepressants: amitriptyline, clomipramine, imipramine, desipramine, nortriptyline, fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, venlafaxine, mirtazapine Antipsychotics: haloperidol, thioridazine, perphenazine, risperidone, clozapine, olanzapine, sertindole, aripiprazole Beta-blockers: alprenolol, bufuralol, metoprolol, propanolol, timolol Antiarrhythmics: encainide, flecainide, propafenone Miscellaneous: atomoxetine, codeine, donepezil, galantamine, phenformin, tramadol	Quinidine Thioridazine Fluoxetine Paroxetine Bupropion Duloxetine	None known
CYP3A4	AEDs: carbamazepine, ethosuximide, felbamate, tiagabine, zonisamide Antidepressants: amitriptyline, clomipramine, imipramine, sertraline, citalopram, escitalopram, venlafaxine, mirtazapine, nefazodone Antipsychotics: haloperidol, pimozide, clozapine, risperidone, quetiapine, ziprasidone, sertindole, aripiprazole Benzodiazepines: alprazolam, clonazepam, diazepam, midazolam, triazolam Calcium antagonists: diltiazem, felodipine, nifedipine, verapamil Statins: atorvastatin, lovastatin, pravastatin, simvastatin Immunosuppressants: ciclosporin, sirolimus, tacrolimus Miscellaneous: amiodarone, astemizole, cisapride, clarytromycin, donepezil, erythromycin, ethiniyestradiol, galantamine, levonorgestrel, methadone, ritonavir, quinidine, tamoxifen, terfenadine	Ketoconazole Itraconazole Erythromycin Troleandomycin Nefazodone Grapefruit juice Ritonavir	Rifampicin Barbiturates Phenytoin Carbamazepine St John's wort Glucocorticoids[a] Oxcarbazepine[a] Topiramate[a] Felbamate[a] Rufinamide[a]

Based on refs 21 and 22.
[a]Weaker or tissue-selective inducers.

Africans. Subjects carrying two mutated CYPC9*3 alleles lack almost completely CYP2C9 activity, and, therefore, are unable to metabolize important CYP2C9 substrates such as phenytoin and S-warfarin. The frequency of this genotype is 0.4% in white subjects. Inhibitors of CYP2C9 include sulphaphenazole, amiodarone, fluconazole, fluoxetine, paroxetine, ritonavir and valproic acid. The activity of CYP2C9 isoforms may be induced by administration of rifampicin, barbiturates, phenytoin and carbamazepine.

CYP2C19

CYP2C19 is involved in the biotransformation of phenobarbital, phenytoin, omeprazole, proguanil, diazepam, citalopram and tricyclic antidepressants (demethylation reactions). CYP2C19 also exhibits a clinically important genetic polymorphism. The frequency of the poor metabolizer (PM) phenotype varies from approximately 3% in whites to 12–25% in many Asian populations, while in black Africans PM frequencies vary between 4% and 7%. The defective alleles responsible for the PM phenotype are CYP2C19*2, the most common among whites and Orientals, and CYP2C19*3, found at a frequency of about 12% among Orientals, but almost absent among whites. The activity of CYP2C19 may be inhibited by omeprazole, ticlopidine, ritonavir, fluvoxamine and by the AEDs felbamate, stiripentol, topiramate and oxcarbazepine. Inducers of CYP2C19 include barbiturates, phenytoin, carbamazepine and rifampicin.

CYP2D6

CYP2D6 represents only 2% of the total P450 content in the liver. Nevertheless, CYP2D6 plays an important role in the biotransformation of a variety of drugs including many psychotropic and cardiovascular drugs. To date, however, none of the major AEDs has been found to be metabolized to a significant extent by CYP2D6. This enzyme is commonly polymorphic. CYP2D6 activity ranges from complete deficiency to ultrarapid metabolism. There are 70 known allelic variants of the *CYP2D6* gene. PMs lack CYP2D6 activity and represent approximately 3–10% of whites, but only 1–2% of Orientals. Among extensive metaboliz-

ers (EMs), the catalytic activity varies largely, and a subgroup of subjects with extremely high enzyme activity have been classified as ultrarapid metabolizers (UMs). Three major mutated alleles, CYP2D6*3, CYP2D6*4 and CYP2D6*5, account for 90–95% of the PM alleles in whites. Alleles with duplication or multiduplication of a functional *CYP2D6*2* gene are associated with an increased CYP2D6 activity: the frequency of this condition varies from 1–2% in Swedes to up to 7–10% in Spaniards and southern Italians. Potent inhibitors of CYP2D6 include quinidine, thioridazine, fluoxetine and paroxetine. In contrast to all other CYPs involved in drug metabolism, CYP2D6 does not appear to be inducible, an important consideration in predicting interactions caused by AEDs.

CYP3A4

CYP3A4 accounts for approximately 30% of total CYP in human liver and 70% in small intestine and participates in more than half of all drug oxidation in human liver. CYP3A4 plays an important role in the biotransformation of AEDs, being the primary enzyme responsible for the metabolism of carbamazepine, ethosuximide, tiagabine and zonisamide, and it is also involved in the biotransformation of felbamate. Drugs primarily metabolized by CYP3A4 include immunosuppressants (e.g. ciclosporin and tacrolimus), triazolobenzodiazepines (e.g. alprazolam, midazolam and triazolam), non-sedating antihistamines (e.g. terfenadine and astemizole), calcium antagonists (e.g. diltiazem, verapamil, nifedipine and other dihydropyridines), cholesterol-lowering drugs (e.g. simvastatin and lovastatin), antiarrhythmics (e.g. amiodarone and quinidine) and several steroids (e.g. cortisol, ethinylestradiol and levonorgestrel). CYP3A4 is also involved in the metabolism of a variety of endogenous compounds such as progesterone, estradiol, testosterone and cortisol. As previously mentioned, CYP3A4 and P-glycoprotein are both expressed in enterocytes and hepatocytes and contribute to a major extent to first-pass elimination of many drugs. Furthermore, there is a considerable overlap in substrate and inhibitor/inducer for CYP3A4 and P-glycoprotein. Although CYP3A4 drug-metabolizing activity varies more than 20-fold among individuals, it has a unimodal distribution and does not appear to be subject to genetic polymorphism. Its wide interindividual variability is caused, at least in part, by modulation of CYP3A4 activity by many environmental compounds, including dietary constituents and medications. Compounds that inhibit CYP3A4 activity include azole antimycotics (e.g. ketoconazole and itraconazole), macrolide antibiotics (e.g. erythromycin and troleandomycin), HIV protease inhibitors (e.g. ritonavir and indinavir), nefazodone and some of the furanocoumarin dimers found in grapefruit juice. The hepatic and, possibly, the intestinal CYP3A4 isoforms are induced by glucocorticoids (e.g. dexamethasone), rifampicin, phenobarbital, phenytoin, carbamazepine and St John's wort. Some newer AEDs, such as felbamate, oxcarbazepine, topiramate and rufinamide, appear to exert a selective inducing effect on CYP3A4 activity, at least in some tissues.

Other CYPs

Minor CYP isoforms include CYP2A6, CYP2B6, CYP2C8 and CYP2E1. CYP2A6 and CYP2B6 are involved in minor pathways of valproic acid elimination, CYP2C8 contributes to the metabolism of carbamazepine and CYP2E1 plays a minor role in the oxidative biotransformation of felbamate and phenobarbital.

Uridine diphosphate glucuronosyltransferases

The human uridine diphosphate-glucuronosyltransferases (UDPGTs) are a superfamily of enzymes that catalyse the glucuronidation of a large number of endobiotics (i.e. bilirubin, steroid hormones, thyroid hormones, bile acids and fat-soluble vitamins) and xenobiotics (i.e. drugs, chemical carcinogens, environmental pollutants and dietary substances) [25]. These enzymes are bound to the internal membrane and face the luminal side of the endoplasmic reticulum, mainly in the liver, but also in the kidney, intestine, skin, lung, prostate and brain. Glucuronidation, which is the most common pathway in phase II drug metabolism, transfers glucuronic acid from UDP-glucuronic acid to functional groups on hydrophobic drug molecules or their metabolites to form the corresponding glucuronides. While most substrates undergo glucuronide conjugation after phase I reactions, in some cases (i.e. morphine and valproic acid) direct conjugation proceeds without phase I functionalization of the parent compound. In most cases, glucuronidation abolishes the pharmacological activity, but active and reactive glucuronide metabolites have also been described, as in the case of morphine.

The human uridine-glucuronosyltransferase (UGT) superfamily comprises two families (UGT1 and UGT2) and three subfamilies (UGT1A, UGT2A and UGT2B) [26]. UGT amino acids have been sequenced and, as in the case of the CYP system, a nomenclature based on amino acid similarity has been developed. While few substrates are relatively selective for a specific UGT enzyme, the majority are glucuronidated by multiple UGTs, thereby making it difficult to know which is the predominant isoform responsible for the glucuronidation reaction. As shown in Table 28.2, some AEDs are substrates of UGT enzymes [22,25]. Among the isoforms of the UGT1 family, UGT1A3, UGT1A6 and UGT1A9 are involved in the glucuronidation of valproic acid, while UGT1A4 has been found to be the major isoform responsible for the N-glucuronidation of lamotrigine and retigabine. Among the isoforms of the UGT2 family, the UGT2B7 variant also appears to contribute to the glucuronidation of valproic acid. The expression of individual UGTs is subject to genetic polymorphism and their activity may be inhibited or induced by

Table 28.2 Substrates of the major UGTs.

Enzymes	Substrates
UGT1A1	Bilirubin, atorvastatin, simvastatin, buprenorphine, gemfibrozil, clofibrate
UGT1A3	Atorvastatin, simvastatin, buprenorphine, gemfibrozil, losartan, morphine, valproic acid
UGT1A4	Lamotrigine, olanzapine, retigabine
UGT1A6	Entacapone
UGT1A9	Dapsone, diclofenac, propofol, tolcapone, valproic acid
UGT2B7	Codeine, gemfibrozil, lorazepam, morphine, naloxone, naltrexone, valproic acid, zidovudine
UGT2B15	Phenytoin metabolites

Based on refs 22 and 25.

xenobiotics. In contrast to extensive documentation for CYP-mediated drug interactions, there are fewer data on interactions involving glucuronidation. It is difficult to make mechanistic interpretation of data obtained from clinical studies on UGT-mediated drug interactions. In this respect, a major limitation has been the lack of quantification of the glucuronide metabolite(s), thereby making it impossible to conclude whether there was an effect at the level of glucuronidation. Any substrate of UGT has the potential to competitively inhibit glucuronidation of other substrates metabolized by the same enzyme. Unlike the CYP system, no specific inhibitors of individual UGT isoforms have been identified.

Other drug-metabolizing enzyme systems

Other drug-metabolizing enzymes may be involved in the biotransformation of some AEDs [22,23]. Tissue hydrolases are involved in the metabolism of levetiracetam, while microsomal epoxide hydrolase is responsible for the clearance of carbamazepine-10,11-epoxide, the main and pharmacologically active metabolite of carbamazepine. Mitochondrial β-oxidation is one of the major pathways of valproic acid biotransformation. The new AED zonisamide is partially metabolized via acetylation by a phase II N-acetyltransferase.

Mechanisms of metabolic drug interactions: enzyme inhibition and enzyme induction

Drug interactions involving CYP isoforms and other drug-metabolizing enzymes may result from one of two processes: enzyme inhibition or induction.

Enzyme inhibition

Enzyme inhibition is the most common mechanism that can lead to drug interactions. A large number of compounds may inhibit the activity of drug-metabolizing enzymes, thereby temporarily blocking their activity. As a consequence of enzyme inhibition, the rate of metabolism of a particular agent is decreased, resulting in increased plasma drug concentrations and potential enhancement of its pharmacological effects. The mechanisms of enzyme inhibition can be categorized as reversible (competitive or non-competitive) or irreversible (mechanism-based inactivation) [27,28]. In reversible inhibition, the normal function of the enzyme is resumed after the inhibitor has been eliminated from the body. Conversely, the loss of enzyme activity caused by irreversible inhibition persists even after the elimination of the inhibitor, and *de novo* biosynthesis of the new enzyme is the only means by which activity can be restored.

Reversible inhibition

This type of enzyme inhibition is probably the most common and can be subdivided further into competitive and non-competitive inhibition [27].

Competitive inhibition refers to a mutually exclusive competition between two drugs (the substrate and the inhibitor) for the binding to the catalytic site of the enzyme. Competitive inhibitors can be alternative substrates of the enzyme with higher binding affinity or non-substrates with, nevertheless, high binding affinity. The binding of the inhibitor prevents the substrate from binding to the active site of the enzyme and, therefore, the substrate cannot be metabolized. The amount of enzyme inhibition depends upon the inhibitor and substrate concentration and the relative affinities of the inhibitor and substrate for the active site. This inhibition can be reversed by increasing the concentrations of the substrate. Competitive inhibition is typically a rapid and dose-dependent process [14,15]. The initial effect usually occurs within 24 h from the addition of the inhibitor, though the time to reach maximal inhibition will depend on the elimination half-lives of the affected drug and of the inhibiting agent. When the inhibitor is withdrawn, restoration of baseline (pre-interaction) conditions is also dependent on the rates of the elimination of the affected drug and of the inhibitor. Among commonly used AEDs, valproic acid is the most notable competitive inhibitor of drug metabolism [1–3].

Non-competitive inhibition involves the strong, covalent binding of the inhibitor to another site of the enzyme. Therefore, the substrate can still bind to the active site, but the basic structure of the enzyme is modified and formation of the enzyme–substrate–inhibitor complex results in loss of enzyme activity. With non-competitive inhibition, the time course of the interaction may be more complex, and a significant role may be played by the turnover (re-synthesis) rate of the enzyme.

Irreversible inhibition

This type of enzyme inhibition usually derives from the activation of a drug by CYPs into a reactive metabolic intermediate that binds tightly and irreversibly to the enzyme active site [29]. These metabolic intermediates cause a chemical modification of the haem, the protein, or both as a result of covalent binding of modified haem to protein. This process is called 'mechanism-based inhibition' or 'suicide inhibition' and may result into a severe and long-lasting inactivation. Enzymatic activity can only be restored through *de novo* protein synthesis. The covalent modification of CYP enzymes can also lead to hapten formation and can in some cases trigger an autoimmune response, resulting in toxicological consequences. Mechanism-based inactivation has been described for CYP3A4. To date, the identified clinically important mechanism-based CYP3A4 inhibitors include macrolide antibiotics (e.g. clarithromycin and erythromycin), anti-human immunodeficiency virus (HIV) agents (e.g. ritonavir and indinavir), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers (e.g. verapamil and diltiazem), steroids and their modulators (e.g. gestodene and mifepristone) and several herbal and dietary components.

Enzyme induction

The activity of drug-metabolizing enzymes in the liver and/or other organs may be increased ('induced') by prolonged administration of several exogenous agents including drugs, industrial contaminants, dietary or voluptuary substances, as well as by endogenous compounds [30]. The inducing process involves predominantly CYP isoenzymes, but induction of other drug-metabolizing enzymes has also been documented. From a biological point of view, induction is an adaptive response that protects the cells from toxic xenobiotics by increasing the detoxification activity. Morphologically, enzyme induction may be associated with a proliferation of the smooth endoplasmic reticulum and hepatic hypertrophy.

Although enzyme induction has been known for almost half a century, the molecular mechanisms involved have only recently been elucidated. In most cases, enzyme induction is the consequence of an increase in gene transcription, usually mediated by intracellular receptors, resulting in an enhanced protein synthesis. However, enzyme induction may also occur through non-transcriptional mechanisms by an inducer-mediated decrease in rate of enzyme degradation or by protein stabilization. An example of the latter is the induction of CYP2E1 by alcohol and isoniazid by stabilization of the enzyme protein not involving a receptor-mediated mechanism [31]. Each inducer has specific actions on a given range of drug-metabolizing enzymes, and several mechanisms of induction are often activated to different extents by a single agent. Currently, intracellular receptors have been identified to be involved in enzyme induction including the aryl hydrocarbon receptor (AhR), the constitutive androstane receptor (CAR), the pregnane X receptor (PXR) and the glucocorticoid receptor (GR) [30,32].

Aryl hydrocarbon receptor

Polycyclic aromatic hydrocarbons, such as benzo(*a*)pyrene and 3-methylcholanthrene, are environmental contaminants formed by incomplete combustion of organic matter (i.e. cigarette smoke and charcoal-broiled beef). These agents selectively induce CYP1A1 and CYP1A2. The mechanism of this type of induction, involving the intracellular AhR, has been well characterized [30,32]. In addition to polycyclic aromatic hydrocarbons, certain constituents of cruciferous vegetables, and certain drugs such as omeprazole and rifampicin, appear to induce CYP1A enzymes by the same mechanism.

Constitutive androstane receptor

Phenobarbital is recognized as the prototype of a class of agents known to induce drug metabolism. Many other compounds – including the AEDs phenytoin, primidone and carbamazepine and the antitubercular agent rifampicin – have been shown to stimulate drug-metabolizing enzymes with an induction pattern which overlaps, at least in part, that of barbiturates. The cluster of enzymes induced by phenobarbital and related agents appears to include several CYPs, such as CYP2C subfamily members, CYP3A4, CYP2B6, possibly CYP1A2, but not CYP2D6. In addition, different UGTs and microsomal epoxide hydrolase appear to be induced by these agents. Thus, the drugs metabolized by enzymes subject to phenobarbital-type induction include a major fraction of all drugs undergoing biotransformation. The orphan receptor CAR has been identified as the molecular target and mediator of phenobarbital-type induction. However, the exact mechanisms of this type of enzyme induction remain to be elucidated. It should be pointed out that the molecular mechanism of phenobarbital-type induction may show partial overlap with that of the PXR and GR, which mediate CYP3A4 induction by rifampicin and glucocorticoids.

Pregnane X receptor

This type of induction is mediated by activation of the human PXR. PXR is expressed predominantly in the liver and, to a lesser extent, in the small intestine, and it mediates the induction of CYP3A4, CYP2B and CYP2C enzymes. This nuclear receptor can be activated by numerous structurally different drugs and xenobiotics including rifampicin and hyperforin, an active component of St John's wort.

Glucocorticoid receptor

The GR is activated by glucocorticoids, in particular dexamethasone. GR mediates the induction of a number of CYP isoforms including CYP2C9 and CYP3A4, both directly and indirectly by facilitating CAR- or PXR-mediated pathways.

Unlike enzyme inhibition, which is an almost immediate response, enzyme induction is a slow regulatory process, usually dose and time dependent [23]. The extent of induction is generally proportional to the dose of the inducing agent and, since the process usually requires synthesis of new enzymes, it occurs with some delay after the exposure to the inducing agent. In practice, the time required for induction depends on the time to reach the steady state of the inducing agent (approximately five elimination half-lives) and the rate of biosynthesis of the enzyme(s). Similarly, the time course of de-induction is also gradual and depends on the rate of degradation of the enzyme and the time required to eliminate the inducing drug. Either of these two processes could be the rate-limiting step.

Enzyme induction may have a profound impact on the pharmacokinetics of drugs metabolized by the susceptible enzyme. As a consequence of enzyme induction, the rate of metabolism of a particular agent is increased, thereby resulting in lower plasma drug concentrations and, possibly, a loss of clinical efficacy. Conversely, if the affected drug has an active metabolite, induction may lead to increased metabolite concentrations and enzyme induction may paradoxically increase pharmacological or toxicological activity. Because of the nature of time-dependent processes, enzyme induction may complicate drug dosing regimens and influence therapeutic decision-making in chronic drug therapy. Addition of any potent inducer to, or withdrawal of, a potent inducer from an existing therapy may cause pronounced changes in drug concentrations, leading to failure of drug therapy or adverse effects. The magnitude and timing of these interactions are critical to allow clinicians to adjust dosages in order to maintain therapeutic effects and prevent toxicity. Enzyme induction represents a common problem in the management of epilepsy as various AEDs, in particular phenobarbital, phenytoin and carbamazepine, possess enzyme-inducing properties [1–3].

Predictability of metabolic interactions based on *in vitro* data

The potential for metabolic drug interactions is an important aspect to consider during the development of new drugs. In the past, most drug interaction studies were performed relatively late in phase II and III clinical studies, using a strategy based on the therapeutic indices of drugs and the likelihood of their concurrent use. Since susceptibility of drug interaction is an undesirable property of a drug, such information should ideally have been obtained already in the preclinical phase. More recently, different *in vitro* methods have been developed and have become widely used as screening tools to predict potential drug interactions before a drug reaches the clinical phases of development. The *in vitro* systems

established for assessing drug metabolism and metabolic drug interactions include enzyme-based techniques, such as purified enzymes, recombinant human enzymes and human liver microsomes, and cell-based techniques, such as liver slices, immortalized cell lines and primary hepatocytes. Each method has its advantage and disadvantage, and the readers are referred to other review articles for further information on this topic [33,34].

Two complementary approaches have been developed to predict potential drug interactions *in vivo* based on *in vitro* data: (a) identification of the enzymes (CYP isoforms or other drug-metabolizing enzymes) responsible for the biotransformation of a test drug; and (b) determination of the potential of the test drug to inhibit or induce the activities of the various drug-metabolizing enzymes. The first approach allows prediction of interactions affecting the metabolism of the test compound (i.e. interactions affecting the test drug as a substrate), while the second allows prediction of any effect that the test compound may have on the metabolism of other drugs (i.e. interactions in which the test drug may act as an inducer or an inhibitor).

The test drug as a substrate (target for interactions)

To predict interactions, the individual enzyme system responsible for the biotransformation of a drug must be identified, and its relative contribution to the overall drug elimination assessed. This may be obtained by using a general *in vitro* strategy [27,33] involving assessment of (a) catalytic activity in human liver microsomes; (b) correlation of this activity with markers for known CYP isoforms; (c) catalytic activity in complementary DNA (cDNA)-based vector systems; (d) catalytic activity in purified enzymes; (e) effects of selective inhibitors; and (f) immunoinhibition with monoclonal or polyclonal antibodies against various CYP isoforms. Once the contribution of different isoenzymes to the metabolism of a given drug has been elucidated, prediction of interactions affecting the biotransformation of that drug can easily be made, based on existing knowledge of the influence that other drugs have on the activity of the same isoenzymes. Identification of CYP3A4 as the primary enzyme involved in carbamazepine biotransformation has allowed the understanding of the effects of several drugs on its plasma concentrations. In fact, most of the drug interactions with carbamazepine that have been documented in clinical practice involve CYP3A4 inhibitors or inducers [35].

The test drug as a cause of interactions affecting the metabolism of other drugs

An *in vitro* strategy similar to that previously mentioned to identify enzymes responsible for the metabolism of a given drug may also be applicable for the evaluation of drugs as potential inhibitors of specific enzyme isoforms. By the use of human liver microsomes or individual enzymes, a series of drugs and/or their metabolites can be screened relatively quickly to determine quantitatively their potency in inhibiting reactions considered to reflect specifically the activity of individual enzyme isoforms. *In vitro* assessment of inhibitory interactions is based on calculation of kinetic parameters such as the inhibitor concentration at which the reaction rate is reduced by 50% (IC_{50}) and the inhibition constant (K_i), the detailed description of which is beyond the scope of this chapter. Different *in vitro* systems, including liver slices, immortalized cell lines and primary hepatocytes, may be used to estimate the enzyme-inducing potential of a drug at preclinical level. In general, these experiments are far more complex, time-consuming and expensive [36]. Once it has been established that an AED inhibits or induces the activity of a given isoenzyme, then one can predict that the metabolism of substrates of the same isoenzyme will be correspondingly affected. A good correlation between the ability to inhibit various enzyme systems *in vitro* and the *in vivo* inhibitory interaction profile has been established for valproic acid [37–40].

While it is relatively easy to assess *in vitro* a drug interaction, the correct interpretation and extrapolation of *in vitro* data to the *in vivo* situation requires a good understanding of pharmacokinetic principles and is complicated by other factors [27,41,42] and, for instance, the extent of inhibition or induction of a given pathway, as assessed on the basis of *in vitro* data, does not necessarily imply that the total clearance of the affected substrate *in vivo* will be affected to the same extent. Factors influencing this include the degree of inhibition/induction of the affected pathway *in vivo* (which may not necessarily correspond to the *in vitro* situation, due to intervention of confounding variables), the contribution of the affected pathway to the overall elimination of the substrate, the pharmacokinetic characteristics of the substrate and its route of administration.

Clinical relevance of metabolic interactions

Information on the drug-metabolizing enzyme systems and their substrates, inhibitors and inducers may be of great value for rational prescribing and may help clinicians to anticipate and eventually avoid potential interactions. In fact, co-administration of two substrates of the same enzyme, or co-administration of a substrate with an inhibitor or an inducer, entails the possibility of a drug interaction. As shown in the previous section, not all theoretical drug interactions that are predicted from *in vitro* studies will occur *in vivo*, and, at any rate, some may not be clinically significant. Drug-related, patient-related and epidemiological factors (Table 28.3) must be taken into account when evaluating the potential occurrence and clinical significance of a metabolic drug interaction [3,23]. Taken together, these factors contribute to the large intersubject variability in the extent and magnitude of metabolic drug interactions.

Therapeutic index of the affected drug

In general, interactions affecting drugs with a narrow therapeutic index (e.g. phenytoin, anticoagulants, immunosuppressants or anti-cancer drugs) are more likely to be clinically relevant than interactions affecting drugs with a wider margin of safety.

Role of pharmacologically active metabolites

Many metabolites are biologically active and this needs to be considered when predicting the clinical consequence of a drug interaction. Another factor to be considered is whether metabolites have any enzyme-inducing or -inhibiting effects independent from those of the parent drug. For example, if a metabolite has an inhibiting effect on a given isoenzyme that is not shared by the parent drug, *in vitro* experiments designed to test the enzyme-inhibiting potential of the parent drug may fail to identify a clinically important interaction.

Table 28.3 Factors to be considered when evaluating the clinical implication of a potential metabolic drug interaction.

Drug-related factors	Therapeutic index of the substrate	Interactions affecting drugs with a narrow therapeutic index are more likely to be clinically relevant
	Dose/concentration of the substrate	Changes in plasma concentrations of the affected drug are more likely to be clinically significant if the baseline values are close to the threshold for therapeutic or toxic effects
	Extent of metabolism of the substrate through the affected enzyme (versus alternative metabolic routes)	If the affected enzyme plays a minor role in the overall metabolic elimination, inhibition will not result in an important decrease in drug clearance, while induction may cause a substantial increase
	Role of pharmacologically active metabolites	The presence of pharmacologically active metabolites may complicate the outcome of an interaction; metabolites may also act as enzyme inhibitors or inducers
	Potency of the inhibitor/inducer	A potent effect is more likely to result in an interaction involving most patients
	Dose/concentration of the inhibitor/inducer at the enzyme site	The effects of enzyme inhibitors/inducers are usually dose dependent; low concentrations at the enzyme site may not be sufficient to elicit an interaction
Patient-related factors	Genetic predisposition	Patients with a genetically determined defect of a polymorphic enzyme will not have interactions mediated by inhibition or induction of this enzyme
	Level of risk for toxicity	Elderly subjects or patients with hepatic or renal impairment are more susceptible to drug interactions
Epidemiological factors	Probability of concurrent use	A potential drug interaction is of limited clinical interest if the drugs involved are rarely prescribed in combination

Based on refs 3 and 23.

Extent of metabolism of the substrate through the affected enzyme

For interactions involving enzyme inhibition, a clinically relevant change in the plasma concentration of the affected drug may occur only if the inhibited enzyme is the major pathway of elimination. As most drugs have several metabolic pathways, the inhibition of an enzyme contributing less than 20–30% to the overall clearance of the affected drug will have a limited impact on its disposition. On the other hand, the situation may be totally different for interactions involving enzyme induction. As there is theoretically no limit to the increase in the efficiency of a given metabolic pathway when the corresponding isoenzyme(s) have been induced, enzyme induction could transform an initially minor metabolic pathway into a major contributor to the overall elimination of the drug, with a consequent important increase in its total clearance.

The different susceptibility of felbamate and topiramate to the action of inhibitors and inducers of their metabolism provide a typical example of this situation. Since CYP3A4 plays only a minor role in the metabolism of felbamate, inhibitors of this isoform would be expected to have only minimal effects on the overall clearance of this drug and, in line with this prediction, felbamate pharmacokinetics have been found not to be significantly affected by the potent CYP3A4 inhibitor erythromycin [43]. On the other hand, the total plasma clearance of felbamate is significantly increased and its plasma concentrations are significantly decreased by concomitant treatment with the CYP3A4 inducers phenytoin, phenobarbital and carbamazepine. A similar situation is observed with topiramate, a drug which, in healthy subjects, is primarily excreted unchanged in urine. Because metabolism is of minor importance in the overall clearance of topiramate, no significant changes in its plasma concentration are expected when an enzyme inhibitor is added on in patients receiving topiramate monotherapy. On the other hand, metabolic elimination possibly becomes the major determinant of topiramate disposition in patients treated with inducing drugs, and this may explain the twofold increase in the total clearance of topiramate reported during co-medication with phenytoin [44].

Genetic predisposition

In patients receiving drugs metabolized by a polymorphic enzyme, the effects of inhibitors or inducers may vary between phenotypes/genotypes. Extensive metabolizers are generally more susceptible to enzyme inhibition or induction than poor metabolizers. This has been most clearly documented for CYP2D6: interactions caused by potent inhibitors of this isoform (i.e. quinidine) are not observed in poor metabolizers, who show a genetically determined lack of functional CYP2D6 in their liver. Similarly, poor metabolizers of CYP2C19 and CYP2C9, who play a role in the metabolism of phenytoin, are not expected to be vulnerable to the inhibition of phenytoin metabolism caused by selective inhibitors of the corresponding enzymes.

Certain metabolic drug interactions are particularly complex and may be difficult to predict where enzyme induction and inhibition occur at the same time. The ability of a given compound to act as both enzyme inducer and inhibitor provides an explanation for the inconsistent and apparently contradictory nature of some drug interactions. For example, at low doses phenobarbital tends to induce the metabolism of phenytoin, probably through induction of CYP2C9 and/or CYP2C19, whereas at higher doses it may competitively inhibit phenytoin metabolism [2]. The extent of these differential interactions may vary across individuals, which may explain the unpredictable and bidirectional changes in plasma phenytoin concentration after addition or removal of phenobarbital therapy. Even more complex is the interaction between phenytoin and warfarin. When phenytoin is started in a patient stabilized on warfarin therapy, phenytoin may initially competitively inhibit the metabolism of warfarin because both phenytoin and S-warfarin are substrates for CYP2C9. After an

initial increase, the plasma concentration of S-warfarin will then decline within 1–2 weeks because of CYP2C9 induction [45]. Other complex situations may arise in patients receiving combinations of three or more drugs. In some cases, the opposite effects of an enzyme inhibitor and an enzyme inducer may cancel out reciprocally. In this respect, the clearance of lamotrigine is markedly increased by co-administration of enzyme-inducing AEDs (e.g. phenobarbital, carbamazepine and phenytoin) and inhibited by valproic acid. However, lamotrigine clearance values in triple-therapy regimens which included valproic acid and an enzyme inducer are similar to those observed in patients on lamotrigine monotherapy [23].

Antiepileptic drugs and metabolic interactions

AEDs may be involved in metabolically based drug interactions because they act as inhibitors or inducers of various drug-metabolizing systems or because they are substrates for the same enzymes. The effect of AEDs on the most common drug-metabolizing enzyme systems is reported in Table 28.4, while the elimination pathways and protein binding for AEDs are shown in Table 28.5.

Table 28.4 Effects of antiepileptic drugs (AEDs) on the most common drug-metabolizing enzyme systems.

Drug	Effect	Enzymes involved
Older AEDs		
Phenytoin	Inducer	CYP2B6, CYP2C, CYP3A UGT Epoxide hydrolase
Phenobarbital/ primidone	Inducer	CYP2B6, CYP2C, CYP3A UGT Epoxide hydrolase
Carbamazepine	Inducer	CYP2B6, CYP2C, CYP3A, CYP1A2 UGT Epoxide hydrolase
Valproic acid	Inhibitor	CYP2C9 UGT1A4, UGT2B7 Epoxide hydrolase
Ethosuximide	None	
Newer AEDs		
Felbamate	Inhibitor Inducer	CYP2C19 β-oxidation CYP3A4
Gabapentin	None	
Lamotrigine	None or weak inducer	UGT
Levetiracetam	None	
Oxcarbazepine	Inhibitor (weak) Inducer (weak)	CYP2C19 CYP3A4 UGT
Pregabalin	None	
Rufinamide	Inducer (weak)	CYP3A4
Stiripentol	Inhibitor	CYP1A2, CYP2C19, CYP3A4
Tiagabine	None	
Topiramate	Inhibitor (weak) Inducer (weak)	CYP2C19 CYP3A4 β-oxidation
Vigabatrin	None	
Zonisamide	None	

Based on [23].

Antiepileptics as inhibitors of metabolic enzymes

Valproic acid is considered to be a broad-spectrum inhibitor of various drug-metabolizing enzymes. Studies in human liver microsomes have documented that, at clinically relevant concentrations, valproic acid competitively inhibits the activity of CYP2C9, inhibits only weakly CYP2C19 and CYP3A4, and has no appreciable effect on CYP2D6 and CYP2E1 [37]. This is consistent with clinical evidence that valproic acid may significantly increase the plasma concentrations of CYP2C9 substrates including the AEDs phenytoin and phenobarbital [40]. *In vitro* studies have indicated that valproic acid may also inhibit epoxide hydrolase, which explains its ability to increase the plasma concentration of carbamazepine-10,11-epoxide in carbamazepine-treated patients, without any substantial changes in the concentration of the parent drug [38]. Valproic acid is an *in vivo* inhibitor of UGTs. At concentrations that are relevant *in vivo*, valproic acid was found to inhibit the UGT2B7-mediated glucuronidation of zidovudine, but had little or no effect on UGT1A1, UGT1A6, UGT1A9 or UGT2B15 [39]. The clinically relevant interaction between valproic acid and lamotrigine has been attributed to inhibition of UGT enzymes, notably UGT1A4 [40]. Valproic acid has been demonstrated to almost double the half-life and serum concentrations of lamotrigine and this contributes to the increased risk for skin rashes when these two drugs are co-administered. Valproic acid has also been reported to inhibit the glucuronidation of lorazepam [25].

Some of the newer AEDs may at times act as enzyme inhibitors. Topiramate has been reported to be a modest inhibitor of the activity of CYP2C19 *in vitro*, and this may account for the moderate elevation of plasma concentrations of phenytoin observed in a small subset of phenytoin-treated patients given topiramate [46]. Oxcarbazepine is also a weak inhibitor of CYP2C19, which might explain its ability, especially when used at high dosages (>1800 mg/day), to increase by up to 40% the plasma concentrations of phenytoin and, to a lesser extent, phenobarbital [2].

Felbamate is a potent and selective *in vitro* inhibitor of CYP2C19 and may increase plasma concentration of phenytoin [43,47]. Administration of felbamate to patients treated with valproic acid has been shown to significantly decrease the clearance and increase the plasma concentrations of valproic acid, presumably by inhibiting the mitochondrial β-oxidation of valproic acid [48]. Felbamate has also been reported to increase the plasma concentrations of other AEDs such as phenobarbital, clobazam, carbamazepine-10,11-epoxide (concomitantly with a reduction in plasma carbamazepine levels), but the molecular mechanisms of these interactions have not been elucidated [2]. Stiripentol, a new AED used for the treatment of severe myoclonic epilepsy in infancy, is a well-documented *in vitro* inhibitor of various CYPs, namely CYP1A2, CYP2C19 and CYP3A4 [49]. Consistent with this, stiripentol increases the plasma concentrations of a wide variety of AEDs, including phenytoin, phenobarbital, carbamazepine, valproic acid and clobazam [50].

Antiepileptics as inducers of metabolic enzymes

The first-generation AEDs carbamazepine, phenytoin, phenobarbital and primidone are broad-spectrum inducers of a variety of CYP enzymes, including CYP1A2, CYP2C9, CYP2C19 and

Table 28.5 Elimination pathways and protein binding for older and newer antiepileptic drugs (AEDs). Fraction of absorbed dose cleared by metabolic and renal elimination refers to average values described for patients on monotherapy. CYP and UGT isoforms responsible for metabolic clearance of each drug are shown in brackets (bold characters identify enzymes involved in metabolic pathways responsible for a major proportion of total drug clearance).

Drug	Proportion of drug eliminated (%) by				Protein binding (% bound)
	CYP	UGT	Other metabolism	Renal	
Older AEDs					
Carbamazepine	75 (**CYP3A4**,CYP2C8, CYP1A2)	15	Negligible	<5	75
Ethosuximide	70 (**CYP3A4**)	No	Negligible	20	0
Phenobarbital	30 (**CYP2C9**, CYP2C19, CYP2E1)	Negligible	25 (N-glucosidation)	25	50
Phenytoin	90 (**CYP2C9**, **CYP2C19**)	No	Negligible	<5	90
Valproic acid	10 (CYP2C9, CYP2A6, CYP2B6)	40 (various UGT)	35 (β-oxidation)	<5	90
Newer AEDs					
Felbamate	15 (CYP3A4, CYP2E1)	10	25 (hydrolysis)	50	30
Gabapentin	No	No	No	100	0
Lamotrigine	No	>80 (**UGT1A4**)	Negligible	10	55
Levetiracetam	No	No	30 (hydrolysis)	70	<10
Oxcarbazepine[a]	<5	60%	No	30	40
Pregabalin	No	No	No	100	0
Tiagabine	90 (**CYP3A4**)	No	Not identified	<2	96
Topiramate	<25	No	Not identified	75	15
Vigabatrin	No	No	No	100	0
Zonisamide	50 (**CYP3A4**)	Negligible	20 (acetylation)	<30	40

Based on refs 1 and 23.

[a]Data refer to the active monohydroxycarbazepine derivative (MHD). Oxcarbazepine is transformed to MHD by ketoreduction catalysed by cytosolic arylketone reductase.

CYP3A4, as well as UGTs and microsomal epoxide hydrolase [1–3]. The time-course of induction and deinduction differs between enzyme-inducing AEDs [14,15]. Induction by phenobarbital starts after approximately 1 week, with maximal effect occurring after 2–3 weeks following initiation of therapy. De-induction follows a similar time-course. With phenytoin, maximal induction or de-induction occurs approximately 1–2 weeks after initiation or removal of therapy. Carbamazepine significantly induces its own metabolism (autoinduction) and, as a result of this, its plasma clearance more than doubles during the initial weeks of therapy. Carbamazepine autoinduction should be completed within approximately 3–5 weeks. Consistent with their enzyme-inducing properties, these AEDs have been reported to increase the clearance and reduce plasma concentrations of many different compounds including other concurrently administered AEDs [1–4]. Clinically relevant interactions should be expected when enzyme-inducing AEDs are given in combination with drugs with a low therapeutic index such as oral anticoagulants, oral contraceptives, immunosuppressants or chemotherapeutic agents [1]. When active metabolites are formed, enzyme induction may result in potentiation of therapeutic and/or toxic effects. Furthermore, these AEDs may induce endogenous substrates including sexual and thyroid hormones and vitamin D [51]. As patients with epilepsy may experience a wide variety of long-term endocrine effects including sexual/reproductive disorders, bone metabolism disturbances and thyroid abnormalities, it has been suggested that this may be related, at least in part, to the use of enzyme inducers. The decreased propensity of most newer AEDs to enzyme induction makes it likely that they may have less effect on the endocrine systems.

In addition to classical enzyme-inducing AEDs, some newer agents, namely felbamate, oxcarbazepine and topiramate, may produce significant enzyme induction, though the spectrum of enzymes induced by these agents appears to be more restricted. Felbamate can induce the activity of CYP3A4, as indicated by a decrease in the plasma concentrations of CYP3A4 substrates such as carbamazepine [43,52]. Unlike carbamazepine, oxcarbazepine is not subject to autoinduction, but can selectively induce the specific isoforms of the CYP3A group involved in the metabolism of oral contraceptives and dihydropyridine calcium antagonists [53]. Oxcarbazepine may also induce UGTs, as suggested by a significant acceleration of lamotrigine clearance [54]. Topiramate is also a weak inducer of CYP3A4, because at dosages above 200 mg/day it may decrease plasma concentrations of ethinylestradiol with a risk of failure of contraception [55]. At lower dosages, topiramate does not appear to affect the metabolism of steroid contraceptives, reinforcing the important concept that enzyme induction is a dose-dependent phenomenon [56]. Recent evidence indicates that rufinamide, a new AED used as adjunctive therapy for the treatment of seizures associated with Lennox–Gastaut syndrome, can act as inducer of CYP3A4 as it can cause a reduction in plasma concentrations of oral contraceptives and triazolam [57].

Antiepileptics as substrates for metabolic enzymes

All commonly used AEDs, except gabapentin, pregabalin, levetiracetam and vigabatrin, are metabolized in the liver by CYPs or UGTs and their biotransformation can be affected by concomitant administration of drugs including other AEDs with inhibiting or inducing properties towards these enzymes.

As CYP2C9 and CYP2C19 are the major isoenzymes participating in the metabolism of phenytoin, it can be anticipated that co-administration of any drug that inhibits these two isoforms will decrease the clearance of phenytoin and increase its plasma concentrations [58]. Interactions consistent with inhibition of CYP2C9 can be caused by, for example, amiodarone, phenylbutazone, fluconazole, miconazole and valproic acid, while interactions consistent with inhibition of CYP2C19 are those caused by ticlopidine, omeprazole, felbamate and topiramate. Isoniazid non-competitively inhibits the metabolism of phenytoin, but it is not clear which CYP enzyme is involved. Other enzyme-inducing AEDs, such as phenobarbital and carbamazepine, have limited effects on plasma phenytoin concentrations as they can also inhibit its metabolism.

CYP2C9 and CYP2C19 are also the major isoforms responsible for phenobarbital biotransformation. However, since each phenobarbital metabolic pathway contributes no more than 20–30% of its total clearance, it can be expected that only broad-spectrum inhibitors could produce clinically relevant effects on phenobarbital elimination. In line with this prediction, valproic acid may cause an up to twofold increase in phenobarbital concentrations, presumably by inhibiting at the same time the CYP2C9-mediated para-hydroxylation and the UGT-mediated N-glucosidation [59]. Potent enzyme-inducing AEDs, such as carbamazepine and phenytoin, have limited effects on phenobarbital metabolism and usually do not modify its plasma concentrations.

CYP3A4 is the primary isoform responsible for carbamazepine metabolism and this information is sufficient to explain the clinically significant elevation in plasma carbamazepine concentrations associated with co-administration of different compounds known to inhibit CYP3A4 activity such as troleandomycin, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, nefazodone, fluoxetine, fluvoxamine, propoxyphene, danazol and ritonavir [35]. Induction of this isoform also explains the decrease in plasma carbamazepine levels caused by phenytoin, phenobarbital and felbamate.

The metabolism of valproic acid involves a variety of processes including direct glucuronide conjugation, mediated by UGT, mitochondrial β-oxidation and minor CYP-dependent oxidation, mainly mediated by CYP2C9 [16]. Because of the multiplicity of pathways of valproic acid metabolism, drug interactions resulting in increased plasma concentrations are complex and often multifactorial. As already reported [48], the new AED felbamate may significantly increase its plasma concentrations, presumably by inhibition of the β-oxidation pathway. On the other hand, valproate plasma concentrations are decreased in the presence of CYP2C9- and UGT-inducing drugs such as the AEDs phenytoin, phenobarbital and carbamazepine. Activation of UGT by carbapenem antibiotics is the most likely mechanism involved in the reduction of plasma levels of valproic acid during co-medication with these antibiotics [11].

CYP3A4 contributes to the metabolism of ethosuximide, felbamate, tiagabine and zonisamide, and induction of this isoform is consistent with the decrease in plasma concentrations of plasma levels of these drugs in patients treated with classical enzyme-inducing AEDs [1–3]. As oxidative metabolism is of minor importance in the overall clearance of topiramate, significant interactions resulting from inhibition are unlikely. On the other hand, metabolic elimination becomes an important determinant of topiramate clearance in patients treated with enzyme-inducing AEDs, an observation which explains the ability of the latter to decrease plasma topiramate concentration by 40–50% [44].

Lamotrigine is primarily metabolized via N-glucuronidation by UGT1A4. This enzyme is inhibited by valproic acid and induced by classical enzyme-inducing AEDs. Consistent with this, valproic acid may cause a significant increase in the plasma concentrations of lamotrigine, and, conversely, concomitant treatment with phenobarbital, phenytoin or carbamazepine results in reduced lamotrigine concentrations [1–3].

Oxcarbazepine is essentially a prodrug for the active 10-monohydroxy derivative resulting from reduction by a cytosolic reductase. This metabolite is subsequently glucuronidated and its levels are decreased in patients receiving enzyme-inducing AEDs [53].

Excretion

Excretion of AEDs is largely mediated by the kidneys. Although drug interactions at the renal level are rare, compounds that undergo extensive renal elimination in unchanged form may be susceptible to interactions affecting the excretion process, particularly when it involves active transport mechanisms or when the ionized state of the drug is highly sensitive to changes in urine pH [60]. This might particularly affect gabapentin, pregabalin, vigabatrin, levetiracetam and topiramate, which are eliminated predominantly through the kidneys, but it has not been established whether this occurs by active transport systems [6]. On the other hand, agents that cause alkalinization of urine (i.e. ammonium chloride) may increase the excretion of acidic drugs such as phenobarbital by reducing their reabsorption from the renal tubules. This effect can be exploited therapeutically in severe cases of barbiturate intoxication [6].

Pharmacodynamic interactions

Pharmacodynamic interactions take place directly at the site of action of a drug or indirectly by interfering with other physiological mechanisms [2]. They result in a modification of the pharmacological action of a drug without any change in the plasma concentration and are more difficult to identify and measure than pharmacokinetic interactions. These interactions can be additive (i.e. equal the sum of the effects of the individual drugs), synergistic (i.e. combined effects are greater than expected from the sum of individual effects) or antagonistic (i.e. combined effects are less than additive) and can be associated with beneficial effects or increased toxicity. Pharmacodynamic interactions involving AEDs have been well documented in experimental animal studies, but limited information is available on their occurrence and magnitude in humans, given the complexity of quantifying dose–response relationships in the clinical setting [61].

Combinations of AEDs can result in increased efficacy, but also a higher risk for toxic effects. The mode of action of marketed AEDs involves different mechanisms including sodium channel blockade, calcium channel blockade, inhibition of

GABAergic transmission and potentiation of glutamatergic transmission. In general, combinations of AEDs acting by different mechanisms would be expected to be more beneficial than combinations of drugs sharing the same mechanism of action [62]. Concerning potentially favourable interactions, clinical evidence does indicate that the combination of valproic acid with ethosuximide or with lamotrigine may lead to seizure control in patients refractory to the highest tolerated does of either drug given alone [1]. Conversely, there are many examples of undesirable pharmacodynamic potentiation of toxic effects that can occur when AEDs are co-administered. Association of drugs that enhance GABAergic inhibition, such as valproic acid and phenobarbital, may result in profound sedation that cannot be explained by pharmacokinetic interactions [61]. The combination of carbamazepine with lamotrigine or with oxcarbazepine has been reported to cause additive neurotoxic effects, such as dizziness, diplopia and ataxia, presumably explained by their common action in blocking voltage-dependent sodium channels [1]. Combination of AEDs may also increase the likelihood of an idiosyncratic toxic reaction. This is the case of the rare occurrence of an acute encephalopathy, characterized by a change in mental status that can evolve to stupor or coma, described in some patients given valproate in combination with other AEDs, particularly phenobarbital. Moreover, AED polypharmacy may occasionally result in seizure exacerbation and an improvement in seizure control is not uncommon when their drug load is reduced [3].

Potentially adverse pharmacodynamic interactions may also occur between AEDs and other drugs, in particular other central nervous system (CNS) agents. Concomitant administration of sedative AEDs (i.e. barbiturates and benzodiazepines) with CNS depressants such as alcohol, antihistamines, tricyclic antidepressants and phenothiazines can potentiate CNS depression, thereby impairing psychomotor and cognitive function, especially in an elderly population [61]. A number of AEDs, particularly those with mood-stabilizing properties (i.e. carbamazepine, valproic acid and lamotrigine), are increasingly used in the management of psychiatric disorders and often in combination with lithium, antidepressants or antipsychotics. There is some evidence that the combination of carbamazepine with lithium may lead to an increased incidence of neurotoxic symptoms such as confusion, drowsiness, lethargy, tremor and cerebellar signs, especially in patients with pre-existing CNS disease [63]. Although the combination of lithium and valproate is generally well tolerated and effective in treating bipolar disorder, additive adverse reactions such as weight gain, sedation, gastrointestinal complaints and tremor have been reported in some patients [63]. Concomitant administration of valproic acid with the second-generation antipsychotics clozapine or olanzapine appears to be relatively safe, although it may be associated with additive side-effects including weight gain and drowsiness [63]. On the other hand, concurrent treatment with carbamazepine and clozapine is generally contraindicated due to concerns about potential additive adverse haematological side-effects [63].

Pharmacodynamic interactions between AEDs and other drugs are poorly characterized. A well-documented case is the interaction between AEDs and non-depolarizing neuromuscular blockers (NDNMBs) [64]. Acutely administered AEDs may potentiate the neuromuscular effects of NDNMBs as a result of direct pre- and postjunctional effects. Conversely, long-term AED therapy may cause resistance to NDNMBs, due to a combination of effects such as enzyme induction and up-regulation of acetylcholine receptors. Another example is represented by combined treatment of pivmecillinam, a pivaloyl-conjugated antibiotic, and valproic acid, which has been reported to cause a hyperammonaemic encephalopathy, presumably due to reduced serum carnitine concentration, induced by the two drugs via independent and possibly additive mechanisms [65].

Drug interactions in vulnerable patient groups and special conditions

Children

Although monotherapy is the strategy of choice for the majority of paediatric patients with epilepsy, co-medication is often needed for patients with pharmacoresistant epilepsy [66]. Treatment of epilepsy in the neonate and child requires an understanding of the peculiar biochemical and pharmacological characteristics of this age range. All pharmacokinetic processes can be markedly affected by maturation and development [67]. Absorption and distribution alterations seem to be confined mostly to neonates and infants, who exhibit a delayed gastrointestinal absorption and reduced concentrations of drug-binding proteins, such as albumin and α_1-acid glycoprotein. The efficiency of elimination processes also changes markedly during development. Renal function at birth is 25–30% of adult values, increasing to 50–75% by 6 months and reaching full maturation at 2–3 years of age. The activity of drug-metabolizing enzymes, notably CYPs and UGTs, is reduced in newborns, particularly in the premature, but increases rapidly in postnatal life, and by 2–3 years of age the metabolic capacity is usually higher than in adults. However, the pattern of enzyme maturation varies between enzyme isoforms and within individuals, resulting in a large pharmacokinetic variability [67].

The combined influence of ageing and co-medication can significantly influence susceptibility to clinically important drug interactions. In this respect, concomitant treatment with valproic acid may increase the risk of lamotrigine-induced hypersensitivity. Lamotrigine is cleared by glucuronide conjugation and only minor amounts are converted by CYP enzymes to an arene oxide intermediate. In infants and children, the reduction of glucuronide conjugation and the faster rates of CYP-mediated reactions, compared with those of adults, can result in increased production of reactive metabolites, which may explain the greater susceptibility to lamotrigine-induced skin rashes in this age group [68]. The inhibition of lamotrigine glucuronidation caused by valproic acid can further increase the formation of reactive oxide intermediate through the alternative CYP-mediated pathways and, therefore, the risk of lamotrigine-induced hypersensitivity, particularly when the lamotrigine starting dose is not reduced and its titration rate slowed appropriately [69]. Another example of an idiosyncratic reaction which may occur more frequently in children on combined AED therapy is provided by the enhanced hepatotoxicity of valproic acid in young patients concurrently treated with enzyme

inducers, possibly related to accelerated formation of reactive oxidation products [69,70].

Elderly patients

Drug interactions in the elderly are usually more frequent and severe than those in younger subjects [71]. In fact, the large inter-individual variability in drug response resulting from genetic, pathophysiological and environmental factors affecting pharmacokinetics and pharmacodynamics is further amplified in the elderly because of the effect of age-related changes, co-morbid disorders and multiple therapy. As a consequence, any given dose of a drug may produce a different, and sometimes unexpected, response, adverse effects and drug interactions in elderly patients. There are various factors associated with the use of AEDs in the elderly that substantially increase the risk of clinically relevant drug interactions [72,73]. These include polypharmacy and age-related changes in pharmacokinetics and pharmacodynamics.

Polypharmacy

AEDs are frequently prescribed in the elderly due to the high prevalence of epilepsy and other AED-treatable neuropsychiatric disorders in this age group. Elderly patients on AEDs, therefore, often take many medications simultaneously, and the probability of both pharmacokinetic and pharmacodynamic drug interactions increases significantly with the number of medications a person takes. Several studies in different settings have unequivocally indicated that the number of prescriptions (and not the age) is the best predictor of adverse drug reactions [74]. Moreover, elderly patients often self-medicate with over-the-counter preparations and natural remedies (herbal products), which also increase the risk of drug interactions. In this respect, in a study in elderly nursing home residents receiving AEDs, the most commonly prescribed co-medications included CNS drugs, cardiovascular agents and anticoagulants, all of which have the potential to interact with AEDs [75].

Age-related changes in pharmacokinetics and pharmacodynamics

Ageing results in the progressive loss of cellular, organ and system functional reserves and thus in changes in pharmacokinetics and pharmacodynamics. Many age-related physiological changes are known to affect drug absorption, distribution, metabolism and excretion [76]. Moreover, medical conditions common in the elderly, such as cardiovascular, renal or gastrointestinal diseases, further alter drug disposition. While drug absorption is generally not significantly influenced by age, changes in body composition may affect drug distribution in the elderly. In particular, the decrease in total body mass with age is associated with an increase in the proportion of body fat. These alterations may lead to increased volume of distribution of lipid-soluble drugs, as the vast majority of CNS drugs are, which tend to accumulate and persist longer in the body. Older subjects may also undergo a gradual reduction in serum albumin, which may result in a decreased protein binding. However, the most relevant age-related pharmacokinetic modifications involve drug elimination, through hepatic metabolism and/or renal excretion. Hepatic metabolic capacity and renal function decline progressively with age. The decline in drug metabolism is mainly explained by changes in liver blood flow and liver mass, while it is still controversial if there is an age-dependent decrease in microsomal enzyme activity [77,78]. These age-related changes in hepatic drug metabolism are unpredictable and difficult to estimate. Changes in renal clearance are more predictable, as glomerular filtration rate decreases by approximately 10% per decade of life beginning at the age of 40 years. The reduced drug clearance may lead to higher and more variable steady-state plasma concentrations. As pharmacological effects, including the inhibitory/inducing effects on drug-metabolizing enzymes, are often concentration dependent, the likelihood of drug interactions is increased in the elderly. Published reports of pharmacokinetics of older and newer AEDs in elderly have been reviewed [67,73].

Although age-related pharmacodynamic changes may be even more important than pharmacokinetic modifications, the pharmacodynamic alterations have been less extensively investigated. Even if the pharmacokinetics of a drug are not modified, an elderly patient may require a smaller dosage because of a change in pharmacodynamic sensitivity. This can produce either a narrower therapeutic range or a shift downward in the lower and upper limits of the range. Elderly patients treated with AEDs appear to be more sensitive to the effects of centrally active drugs, even when plasma concentrations are controlled, as documented in a controlled clinical trial comparing the efficacy and safety of carbamazepine and valproic acid. Patients over 65 years of age experienced side-effects at concentrations of carbamazepine and valproic acid of 50% and 20%, respectively – lower than in younger subjects [72].

Pregnancy

The use of AEDs in women of child-bearing age requires special consideration with respect to fertility, contraception and pregnancy.

Prescription of oral contraceptives in women with epilepsy is relatively common and may be associated with clinically important drug interactions [1]. CYP3A4 is involved in the metabolism of both endogenous and exogenously administered oestrogens and progesterones. Various AEDs (i.e. carbamazepine, phenytoin, phenobarbital, primidone, felbamate, oxcarbazepine and rufinamide) stimulate the metabolism of steroidal oral contraceptives, thereby reducing the efficacy of the contraceptive pill, with the potential for unwanted pregnancy [1,57]. Topiramate might also induce the metabolism of steroid contraceptives, but only at doses >200 mg/day [55]. Other AEDs, including valproic acid, ethosuximide, lamotrigine, gabapentin, tiagabine, levetiracetam and zonisamide, do not affect the metabolism, and therefore the efficacy, of oral contraceptives. With lamotrigine, however, a reciprocal interaction has been documented, in which oral contraceptives induce the metabolism of lamotrigine and decrease its plasma concentrations by approximately 50% [1]. Therefore, women with epilepsy taking lamotrigine need to be monitored carefully for seizures when oral contraceptives are started and for signs of toxicity when they are discontinued.

Concomitant administration of different AEDs to pregnant women with epilepsy may increase the risk of congenital malformations in newborns. Results of large-scale studies, including collaborative multinational registries, have indicated that AED

monotherapy with the most commonly used AEDs is associated with a two- to threefold increase in risk of major congenital anomalies compared with the general population, and that the magnitude of risk increases with increasing number of AEDs administered during the first trimester of pregnancy [79,80]. Information on teratogenic potential of newer AEDs is still limited and it is not known if they enhance the teratogenic potential of older AEDs when prescribed in combination therapy. As the mechanism of teratogenesis may involve the production of epoxide or other toxic metabolite intermediates, it is difficult to differentiate the relative contribution of pharmacokinetic and pharmacodynamic factors in the occurrence of a teratogenic interaction.

Conclusions

Drug interactions represent a frequent complication of AED therapy. The vast majority of pharmacokinetic interactions with AEDs arise as a consequence of drug-induced changes in hepatic metabolism, through enzyme inhibition or induction, and less frequently from changes in plasma protein binding. On the other hand, limited information is available on the occurrence and clinical significance of pharmacodynamic interactions involving AEDs. Based on the available evidence, newer AEDs appear to have a more favourable drug interaction profile than older compounds.

Wherever possible, drug interactions with AEDs should be prevented by avoiding the unnecessary use of multiple drug therapy. In recent years, an improved understanding of the mechanisms involved, in particular increased knowledge of the specific enzymes responsible for the metabolism of each individual AED and the effects of these compounds on the activity of the same enzymes, has allowed a more rational approach to prediction and management of drug interactions. In most cases, adverse clinical consequences of drug interactions may be anticipated and minimized by appropriate dosage adjustments based on close evaluation of clinical effects and, possibly, plasma drug concentration monitoring.

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29 Medical Treatment of Epilepsy in Situations with Limited Resources

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Global burden and distribution of epilepsy

An estimated 40 million people worldwide suffer from epilepsy, with 85% of these individuals residing in resource-poor regions [1]. This disproportionate burden of disease is partly determined by their large populations and the age distribution of these populations, but also reflects a heavy burden of traumatic brain injury, poor antenatal services, high incidence of central nervous system (CNS) infections and the very limited capacity of developing country systems to provide basic resources including adequate nutrition, safe drinking water, and preventive and primary health-care services. The implementation of simple measures such as vaccination programmes, the training of traditional birth attendants, and enforced helmet and seatbelt laws are cost-effective approaches to preventing insult and injury to the nervous system throughout the life-course of individuals. For our purposes, 'resource-limited setting' refers not only to limited resources for *care*, but also limited resources for *survival*. Much of the material presented here is most applicable to extremely resource-limited settings, including southern Africa. A comprehensive text addressing epilepsy care globally with an emphasis upon developing regions of the world is available [2].

In extremely resource-limited settings, brain disorders are particularly common, but occur within the context of competing needs for fiscal investments into basic services. The individual in resource-limited settings is focused upon food acquisition, the provision of shelter, adequate personal safety, and the maintenance of the social relationships required for survival in such environments. The state is focused upon investments in the development of infrastructure for education, food security, transport, trade and economic development. Regional conflicts and political corruption worsen such situations drastically. As a general rule, the need for neurological health-care services either goes unrecognized or is overtly neglected.

Health systems and neurological services

Wealth largely determines health. Resources for public infrastructure, particularly to provide public health resources such as clean accessible water, are the minimal investments required in addressing the health of the citizenry. Further investments in health services for preventive and curative care are also needed to optimize the health of a population, and individuals within the region must have the personal financial resources to access care. The resources available for health and health care are largely determined by a country's wealth while the distribution of services internally can be predicted by the progressive or regressive nature of income redistribution. Given the neglected nature of neurological illness and service development in resource-poor settings, little was known regarding available services for epilepsy care in many regions until 2004, when the World Federation of Neurology (WFN) produced a comprehensive atlas that delineated the service availability for neurological care [3], followed in 2005 by a similar atlas focused upon epilepsy care resources [4]. These atlases provide a broad range of information from the number of neurologists to the availability of neuroimaging and electroencephalography in all regions of the world. The implications that the data presented in the atlases have for neurological care delivery in most resource-poor settings are profound. Resources for care available to people with epilepsy in very low-income countries (as defined by the World Bank) include a mean of 0.03 neurologists per 100 000 people. Electroencephalography and computed tomography (CT) availability is generally limited to large cities and often only to individuals with personal resources to access and pay for this service. Less than 30% of countries within the African region have magnetic resonance imaging (MRI) technology. Postgraduate training programmes in neurology are generally not available in low-income regions. Within sub-Saharan Africa, only South Africa offers such training and the median number of postgraduates per year specializing in neurology in all of Africa is only 18. The dearth of neurological expertise in such regions is unlikely to improve unless a 'reverse' brain drain occurs, with neurologists from wealthier countries immigrating to these areas, or local training programmes initially staffed by such individuals are established. Regardless, the model in the West of epilepsy care being delivered by neurologists is not a feasible model for epilepsy care provision in resource-poor settings.

In low- to middle-income countries (LMICs, as defined by the World Bank), neurological specialists are often non-existent, and physician-level care is also extremely limited. Most health care is provided by non-physician health-care workers including nurses, midwives and clinical officers. Clinical officers (COs), who receive 3 years of technical training after secondary school (i.e. high school), are the backbone of the health-care system in much of sub-Saharan Africa. To some extent, COs are similar to the 'barefoot doctors' serving regions of Asia and Latin America. While developed regions might consider such non-physician health-care workers 'physician extenders', most non-physician health-care

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workers in resource-poor settings do not have the direct supervision of a physician. In rural regions of Zambia, clinics and even hospitals are staffed without physicians on site and the median distance to the nearest physician is 50 km [5]. Where ox-carts and bicycles are common modes of transport, such travel, particularly for ill individuals or persons with physical disabilities, is almost impossible. Decentralized epilepsy care, delivered as close to the patient as possible, offers the best chance of providing access to basic treatment for most people in the world with epilepsy.

The training curriculum of non-physician health-care workers in LMICs is generally determined by the commonest recognized health-care needs of the population to be served and the expertise of the trainers. As such, the focus is generally on basic primary health care and infectious diseases of public health import. Most training emphasizes vaccinations, maternal and child health-care services, and acute curative care delivery for common treatable conditions such as malaria, pneumonia, sexually transmitted infections and infectious diarrhoea. A 2002 survey of Zambian clinical officers and nurses found seizure to be the most common neurological problem encountered by these individuals. Yet, less than a third of respondents felt they knew how to treat acute seizures, and even fewer were comfortable managing epilepsy [6]. Although this situation probably reflects the ongoing reality in epilepsy care delivery for most resource-poor settings, small investments in health-care workers' education can change this and make basic epilepsy care services available, affordable and feasible to the masses. This has been shown in World Health Organization (WHO) demonstration projects in China and Brazil [7,8], WFN-funded programmes in Zambia and Malawi, and projects in Bamako [9], amongst others. Despite many examples that non-physician health-care workers with inexpensive medications can effectively treat many people with epilepsy at a community-based level, the *epilepsy treatment gap*, meaning the proportion of people who require treatment but are not receiving it, remains between a dismal 80% and >95% in many of the very low-income countries of the world [10].

Aetiology of epilepsy in resource-limited settings

Even in developed countries, we are unable to determine an underlying aetiology for epilepsy in at least 30% of patients assessed, so it should hardly be surprising that in resource-limited settings without recourse to neuroimaging or electroencephalography, we have limited information regarding the aetiology for epilepsy in most people with epilepsy. Furthermore, the individuals who access care and have an evaluation to assess the aetiology of their epilepsy in LIMC are a select few and hardly representative. On a population basis, however, we do have some insights as to what may be among the underlying causes of epilepsy in such regions.

Infections

Central nervous system infections from vaccine-preventable diseases, such as infection with *Haemophilus influenzae* type B, remain common in resource-poor settings. The meningitis belt of Africa has almost annual outbreaks of meningococcal infections. Delays in care seeking and delivery further worsen the neurological prognoses of such infections. Three to four million children in the world suffer from severe malaria annually, and cerebral malaria survivors are at substantial risk of subsequent epilepsy. A retrospective cohort study in Kenya found an odds ratio of 4.4 for epilepsy in cerebral malaria survivors relative to other children in the region [11]. A prospective exposure–control study in Malawi found that almost a third of paediatric cerebral malaria survivors experienced adverse neurological outcomes over 2–3 years of follow-up, with 15% of survivors experiencing unprovoked seizures during an 8–15-month follow-up period [12]. When children in resource-limited settings develop serious illnesses associated with fever, seizure and/or coma, the diagnostic evaluation may be rather limited, and empirical treatment with antibiotics and antimalarials may be given, with little documentation available for later review if, or when, the child develops a subsequent seizure disorder. Careful questioning of the parents regarding any such prior illnesses can elicit helpful data.

Parasitosis, particularly from *Taenia solium* with neurocysticercosis (NCC), is a common cause of epilepsy in Latin America and regions of Africa. Public health measures that improve the management of human waste and regulate animal husbandry practices are needed to decrease NCC rates. Until these occur, acute symptomatic care and chronic management are recommended in addition to seizure management [13]. Schistosomal eggs, usually limited to the gastrointestinal or genitourinary tracts, may occasionally end up in the CNS and produce seizures [14–16]. Some have suggested that onchocerciasis (infection with *Onchocerca volvulus*), which usually results in river blindness, may also be a cause of epilepsy [17–20], but this is still under debate. Other parasitic infections, such as trypanosomiasis, may cause acute seizures, but without treatment are generally fatal and as such will not result in a chronic epileptic condition.

Tuberculosis (TB) and human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), two disorders tightly interlinked in resource-poor settings where the co-epidemics rage on, can also result in epilepsy related to tuberculomas, TB meningitis, HIV-related opportunistic infections, HIV encephalopathy or immune reconstitution syndrome. As antiretroviral therapy (ART) becomes increasingly available, HIV/AIDS as a chronic condition will become more common in LMICs. Studies suggest that 3–11% of people with HIV/AIDS will experience seizures [21,22]. Although no data are available regarding long-term outcomes, we can anticipate an increase in epilepsy prevalence in regions with high HIV/AIDS rates as ARTs continue to roll out.

Traumatic brain injury

The risk of traumatic brain injury (TBI) across the lifespan is greater for people residing in resource-limited settings than in those living in more developed regions for many reasons. Sports-related head injuries occur and helmet availability and use in most resource-poor regions is uncommon. Few protective measures are in place to prevent work-related head injuries from falls or faulty equipment. Bicycles and motorbikes are common modes of transportation, but road conditions are poorly suited for these vehicles. Seatbelts are not typically available in public buses or minibuses. In fact, much of the public transport in rural regions is provided by informal 'taxis', which simply load (and substantially overload!) people and their animals into the back of pick-up trucks (Plate 29.1). In regions with war or internal conflict, head injury

in combatants as well as civilians contributes to the burden of epilepsy. Where war or civil unrest prevails, violence against civilians may result in a greater number of deaths and injuries than the official 'conflict' figures.

Perinatal causes

Central nervous system injury and malformation related to intrauterine infections such as toxoplasmosis and rubella and cytomegalovirus infection remain problematic in LMICs. Frequent maternal infections with associated fevers add additional risks for poor neonatal outcomes. Inadequate access to midwifery and obstetric services also result in higher rates of labour-related hypoxic brain injuries. Improvement in child health and a decrease in under-5 mortality rates are within the United Nations' Millennium Development Goals, but most planned measures will benefit older children rather than neonates. Brain injury rates in the first year of life are unlikely to change as a result of the Millennium Development Goals [23,24].

Other

Whether a general state of physical deprivation contributes to the development of epilepsy remains unclear. The epidemiologic 'life-course' approach to disease [25,26] attempts to quantify the accumulated burden of exposures from conception forward and would offer an ideal approach to considerations of epilepsy aetiology in resource-limited and tropical settings, if data were available. The Barker hypothesis [27] suggests that chronic health conditions, including hypertension and diabetes, are more likely to occur in individuals who have parents or even grandparents who were deprived in their own life-course. Although few data are available to support quantitative analysis using the Barker hypothesis or life-course approach, it seems likely that an accumulated burden of CNS injuries or insults (at least within the individual's lifespan) can predispose to a chronic seizure disorder and that such CNS insults are probably common in resource-poor settings [28–30].

Social context of epilepsy in resource-limited settings

Having epilepsy is more than having seizures. 'Being epileptic' results in psychosocial dysfunction and suboptimal quality of life. For many people with epilepsy, the burden of 'being epileptic', its stigma and its psychosocial consequences outweigh the biomedical burden of the condition. Perhaps nowhere is this more apparent than in resource-limited settings, where epilepsy-associated stigma and its social and economic sequelae have a large impact on people with epilepsy and consequences for their entire household [31–33].

In developing regions where education levels and literacy are relatively low, local beliefs regarding the underlying causes of epilepsy incorporate religious beliefs with issues of possession, blame and witchcraft, and include substantial contagion fears [31–36]. Contagion beliefs, uncontrolled seizures and open fires spell disaster for people with epilepsy in developing regions [37]. High rates of injury and death related to burns and drowning among people with epilepsy are well recognized by epilepsy care providers in such regions. Sadly, such accidents often occur with frightened friends or family members witnessing the event. Comorbid psychiatric disorders, especially depression and anxiety, among people with epilepsy are common.

The social and economic sequelae of epilepsy-associated stigma in resource-poor regions are particularly heavy. Even in relatively developed regions, people with epilepsy suffer from such stigma, but in developed regions this stigma tends to be more felt stigma or internalized stigma, while in less-developed regions stigma is often external and accompanied by gross discrimination [38]. Limited opportunities for education, employment and marriage translate into poorer housing quality, less food security and poorer access to health-care services [32]. Poor housing quality increases exposure to open fire and open bodies of water. Economically, the entire household is disadvantaged. Children with epilepsy reside in poorer households, but are marginalized within the household in terms of access to education and food, relative to their siblings. Social vulnerability for people with epilepsy results in high rates of physical abuse within and rejection from the household. Women with epilepsy are at increased risk of experiencing sexual assault. The social and economic consequences of being a person with epilepsy in a resource-poor setting, if laden with the additional burden of epilepsy-associated stigma, may lead to a steady downward-spiralling decline in terms of social, economic and medical well-being (Fig. 29.1). These circumstances make delivering care to this population extremely challenging.

The role of the neurologist

While much of this text has been dedicated to helping the neurologist determine how to provide *optimal* care to *individuals* with epilepsy, in resource-limited settings the goal is often to determine what epilepsy services are *possible* to deliver to as large a *population* as is possible. Optimal, individualized care may simply not be an option.

Setting the groundwork

Neurologists presently working in resource-poor settings and/or planning to conduct such work should spend some time learning about the local intricacies of the health and health services system. Table 29.1 lists key information that should be obtained to assist in determining where and by whom neurological care services can be best delivered, who to train to provide such care, and what treatment options and ancillary support services can and should be offered to people seeking epilepsy care.

Diagnosis

The neurologist's approach to caring for a person with epilepsy in a resource-poor setting will be largely dictated by what resources are available for care. In terms of diagnostics, neuroimaging may not be available, may be available but at substantial out-of-pocket costs, or may be available to a limited number of publicly funded patients each month. Electroencephalography technology may not be available. Or the quality of the records and review may be so poor as to make the resource essentially obsolete. In the resource-limited setting, history-taking, from the patient as well as close family members, is the most critical and sometimes only diagnostic assessment available.

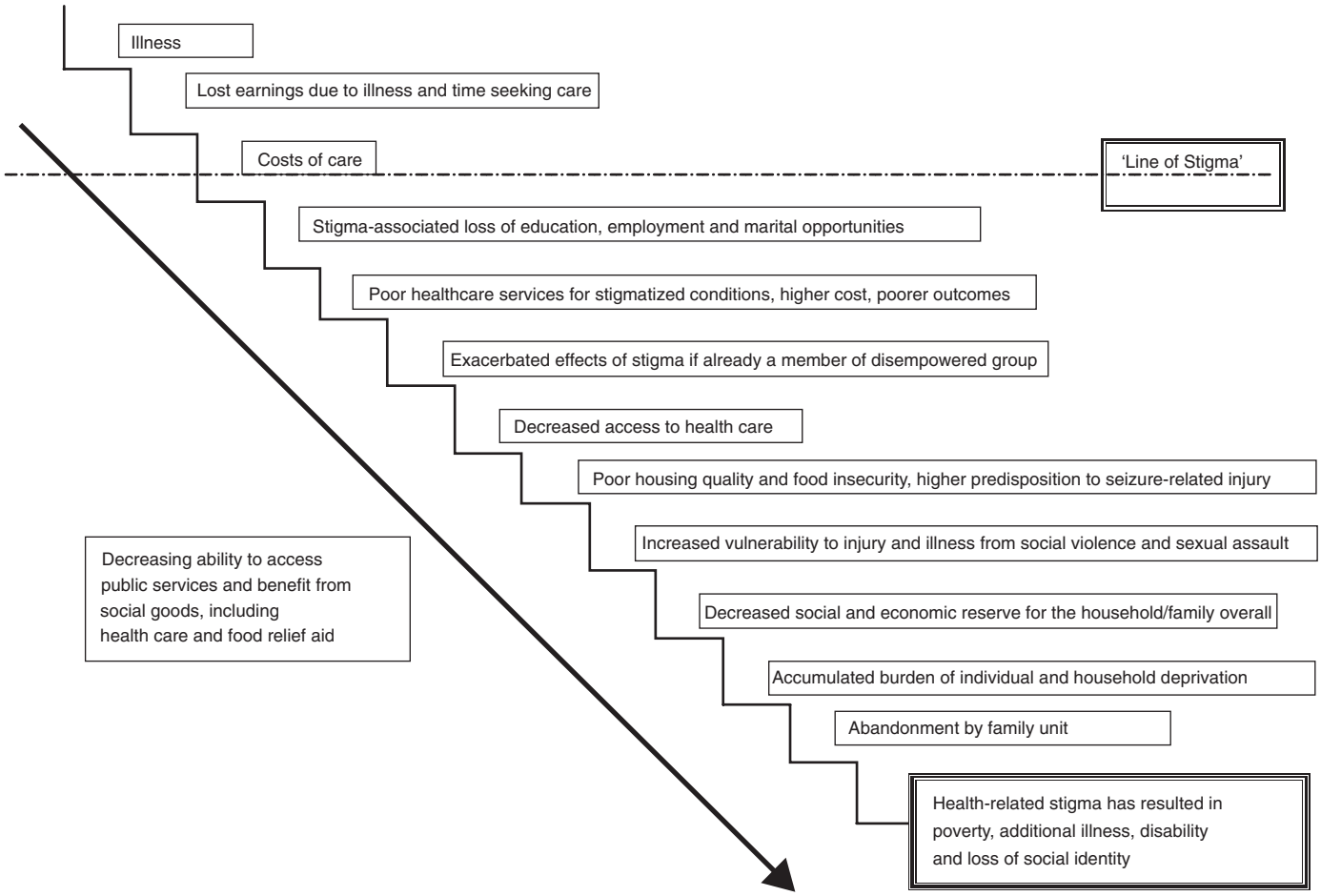

Fig. 29.1 Stigma stairs – the accumulated burden of epilepsy-related stigma.

Treatment

Many LMICs have only phenobarbital available for chronic seizure treatment, with other AEDs not provided by the health system, technically provided but only rarely in stock at local pharmacies, or available but at substantial cost to the patient, who already has a number of competing financial needs to cover his/her basic survival needs. Unless the neurologist is certain that the patient has the resources to purchase other anticonvulsant medications on a long-term basis, phenobarbital should be the initial drug of choice.

Phenobarbital

Dosing

A loading dose of 10–20 mg/kg is needed to achieve therapeutic drug levels. Where intravenous access is limited, loading can be undertaken by dividing the dose into multiple intramuscular injections. Because of its prolonged half-life, by initiating maintenance dosing, it will be more than a week before therapeutic levels are achieved. Maintenance doses of 2–6 mg/kg/day, taken daily in adults, and daily or twice daily in children, are recommended.

Advantages

Phenobarbital is generally cheap, even if purchased out of pocket. As the AED for the WHO essential drugs list, phenobarbital is usually available in government clinics and pharmacies. Dosing parameters and side-effects are more familiar to health-care personnel than other medications for chronic seizure management. Phenobarbital also offers a relatively broad spectrum of activity, being appropriate for use in patients with primary generalized as well as partial-onset seizures.

Disadvantages

Phenobarbital can cause cognitive and behavioural problems, especially in the elderly and young children.

Side-effects

In addition to cognitive and behavioural side-effects, Dupuytren's contracture, facial coarsening and folate deficiency may occur. Abrupt discontinuation of treatment (from either non-adherence or erratic drug supplies centrally) may result in withdrawal seizures, including status epilepticus. Rapid intravenous dosing and/

Table 29.1 Key questions to consider when setting the groundwork for epilepsy services development.

Health system
How is the public system funded?
How is the system organized administratively?
What are the routes and routines for referrals?
What facilities exist for care at each level in terms of primary, secondary and tertiary care centres?
How are priorities and health policies developed?
What user fees are imposed?
What is the quality of care at various levels, including laboratory support?
What diseases/conditions constitute the bulk of what health-care workers see?
What parallel systems of care are there? Private? Faith-based? Traditional?
What medications are provided free? Which others are accessible? Where? And at what cost?
Health-care workers
Who provides primary care? Inpatient care? Antenatal care? And what is their training?
What extenders are used (community health workers, trained birth attendants, etc.) and what is their training?
What neurological education, if any, have the non-physician health-care workers had?
How comfortable and competent are the health-care workers (physician and non-physician) in caring for patients with epilepsy?
Patient-level factors
What barriers to care and adherence do people with epilepsy encounter in the system?
What indirect costs are associated with care seeking and adherence?
What is the average wage? Relative to drugs and indirect costs?
What traditional beliefs regarding epilepsy are commonly held in the region?
How substantial is the burden of epilepsy-associated stigma?

or high loading doses must be avoided where ventilators for respiratory support are not available.

Interactions

Phenobarbital, and in fact all of the enzyme-inducing AEDs, may interact with antiretroviral medications used for HIV/AIDS and could potentially result in subtherapeutic levels of antiretroviral medications, specifically protease inhibitors (PIs) and non-nucleoside reverse transcriptases (NNRTIs) [39]. Phenobarbital can also decrease the efficacy of hormonal contraceptives. Rifampicin, a commonly used TB medication, may lower phenobarbital levels. Interactions with co-administered traditional medicines should be considered.

Other considerations

Decisions regarding when to initiate or discontinue AEDs require careful weighing of the burdens and benefits of the available treatment. Burdens of treatment may include drug side-effects (particularly when treatment options are limited to phenobarbital), extreme efforts required to acquire AEDs for people located in remote regions, and personal and/or family reluctance for daily medication versus occasional seizures.

Other antiepileptic drugs

Carbamazepine, valproic acid and phenytoin may also be available in resource-poor settings, but their consistent availability can be less reliable, especially in non-urban settings. Health-care workers may be less familiar with dosing and potential side-effects for these medications. Laboratory resources for AED drug levels are generally not available. Monitoring of electrolytes and liver functions may also be difficult to assess. Inappropriate use of carbamazepine in persons with unrecognized primary generalized epilepsy can be problematic. Health-care personnel unfamiliar with the zero-order kinetics of phenytoin often make unwise decisions in terms of titrations and dose changes. Several cases of carbamazepine toxicity as a result of antiretroviral medication initiation have been reported [40–42].

Other aspects of care

In addition to diagnosis and treatment, patient and family education and counselling must play a central role in clinical management of epilepsy. Patients and their families must be persuaded of the need for chronic treatment. This can be difficult in a culture of only acute curative care. Educational efforts to alleviate family members' contagion fears and enlist their support for adherence and retention are critical. Families also need to be informed as to what to do when seizures occur (e.g. the recovery position). Counselling regarding the risks to the person with epilepsy for burns, drowning and other injuries may open a dialogue that allows the family to reallocate domestic duties to decrease injury risk. Such counselling sessions can be conducted in groups to optimize the physicians' time. A trained community health worker or nurse can also undertake to lead such discussions once that have been properly educated and provided with medications to dispense.

In developed countries, neurologists provide medical care services with care tailored to the individual's needs. Where there is only one neurologist for every 5–10 million people, this model of care abandons the vast majority of people with epilepsy to care provision by local traditional healers. With such limited neurological expertise, a more effective use of the neurologists' talents is not that of a specialist care provider for a small population of patients but that of a medical educator, policy advisor and community advocate for people with epilepsy.

Medical educator

In resource-limited settings with few neurologists, the neurologist should ideally maintain a strong focus on medical education, including curriculum planning and training of medical students, non-physician health-care workers and continuing medical education for physician-level colleagues. A key limitation is the lack of training tools and educational materials for non-physician health-care workers to provide epilepsy care services independent of physician oversight. Even texts written for general physicians assume a knowledge of anatomy, physiology and pharmacology that exceeds the background education acquired by nurses and clinical officers. Some texts have been developed [43,44]. The thoughtful development of simple algorithms for epilepsy care delivery that utilize available medications in terms familiar to local clinicians can go a long way towards improving the care available for people with epilepsy. The neurologist can also train other physicians who see many people with epilepsy (e.g. internal medicine physicians), and this should substantially improve the quality of care available to people with epilepsy, particularly if these general physicians participate in medical student and postgraduate education.

Policy advisor

Ideally, if a neurologist has become familiar with the health system, health-care workers and patient population in the resource-limited setting in which he/she works, then the neurologist is uniquely positioned to offer policy-makers advice and assistance in developing protocols for care, national guidelines and selecting essential drugs to be made available within each level of care. If involvement in such activities is not spontaneously solicited, service on hospital or clinic committees and/or formal letters of interest and offer to the appropriate persons within the health sector may help foster such opportunities. Contact with embassies can be helpful by facilitating introductions to policy-makers. Often non-governmental organizations also play a substantial role in care delivery and policy development.

Community activist

Even in countries with few neurological experts, organizations affiliated with the International League Against Epilepsy (ILAE) and/or the International Bureau for Epilepsy (IBE) often thrive. The interests of people with epilepsy are also often represented by groups that advocate for the rights and care for people with disabilities. Consulting the ILAE and IBE websites or personnel can help locate support groups.

Researcher

Resources for laboratory-based research are limited in LMICs, but the environment is ideal for implementation and operations research and with some infrastructure development, clinical research (epidemiological as well as clinical trials) is possible. Acquisition of research skills appropriate for use in resource-limited settings requires thoughtful consideration. Standard fellowships and postgraduate training programmes may or may not offer the skills needed. Guidance from groups such as the World Federation of Neurology's Research Committee or the International Brain Research Organization (IBRO) is recommended.

Additional considerations

Paradoxical situations encountered in epilepsy care provision in resource-poor settings include trying to deliver medically advanced services to patients who may be living in very primitive domestic settings (in terms of, for example, housing quality) and who may hold very traditional beliefs regarding their medical condition and health in general. Traditional healers may be their health-care provider of choice [45] and dual, parallel care-seeking practices are common. Historically, traditional healers and physicians have had generally antagonistic relationships, but this is avoidable. Physicians can offer the respect due to traditional healers based upon their social role as 'healers' without endorsing the biomedical efficacy of their treatments.

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3

Section 3
Antiepileptic Drugs

The Treatment of Epilepsy, Third Edition Edited by S. Shorvon, E. Perucca and J. Engel
 ISBN: 978-1-405-18383-3

30 Introduction to the Choice of Antiepileptic Drugs

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Until second-generation antiepileptic drugs started to be introduced in the early 1990s, the pharmacological management of epilepsy was relatively simple. Only a handful of drugs could be prescribed, and making a choice among them was not a major problem. Today, with about 20 different medications available, selection of an antiepileptic drug is a much more complex process. In fact, the existence of a broad pharmacological armamentarium is a mixed blessing. On one hand, since each drug differs from the others, a wide choice of medications means that physicians have unprecedented opportunities to tailor treatment choices to the characteristics of the individual [1]. On the other hand, familiarizing with the indications, contraindications, specific properties and dosing schedules of 20 different drugs is no easy task, and there are concerns that suboptimal knowledge could result in incorrect prescribing and related harmful consequences. Keeping up to date with rapidly expanding knowledge is a challenge for every practitioner, and easy availability of information in the electronic age does not necessarily imply ready access to high-quality, unbiased documentation.

In the era of evidence-based medicine, drug selection should be best guided by an assessment of the comparative benefits to risks ratios of available treatments, based on results of well-conducted, randomized double-blind trials. Unfortunately, a fully evidence-based approach to the treatment of epilepsy is hampered by the fact that the vast majority of randomized active-control trials in this area have significant methodological shortcomings, including recruitment of populations poorly defined in terms of syndromic diagnosis, insufficient sample size, suboptimal dosing regimens and bias in study design which may have favoured the sponsor's product [2–4]. Additionally, therapeutic outcome in many epilepsy syndromes has never been evaluated in controlled trials. Because of this, drug choice cannot be based solely on results of therapeutic trials, and a broader range of information must be taken into account. In fact, none of the available medications can be recommended as the treatment of choice for all patients, and rational prescribing requires a critical assessment of both the properties of each drug and the characteristics of the patient (Table 30.1). The overall objective is to select the treatment which provides the best match for the characteristics of the individual, and ensures the highest probability of achieving seizure freedom without causing undue adverse effects [5].

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The purpose of this chapter is to highlight the main factors to be considered in choosing an antiepileptic medication, while the properties of each of the major drugs are discussed in the subsequent chapters. The rational approach to the management of adults and children with newly diagnosed seizure disorders, as well as individuals with chronic active epilepsy and other specific categories of patients, are discussed in Part 2 of this volume.

Spectrum of efficacy in relation to seizure types and epilepsy syndromes

Most randomized trials of antiepileptic drugs have been conducted in patients with partial seizures, and very few controlled studies have assessed the potential efficacy of these medications in generalized seizure types, or in specific epilepsy syndromes [3,6,7]. As a result, information on the spectrum of efficacy of individual drugs in generalized seizures derives mostly from uncontrolled studies and clinical experience, including the opinion of experts [8–10]. Despite these methodological limitations, there is clear evidence that antiepileptic drugs differ markedly in their spectrum of efficacy in various seizure types (Table 30.2).

Based on available data, drugs can be differentiated into so-called broad-spectrum agents, which are effective against partial seizures and several primary generalized seizure types, and agents whose efficacy spectrum is restricted to very few seizure types (Table 30.2) [1,8–10]. The latter include a group of drugs which are mostly useful in the treatment of focal epilepsies, the relatively selective anti-absence drug ethosuximide, and the drugs used primarily to treat infantile spasms, e.g. vigabatrin (which is also efficacious against partial seizures, but which is rarely used in this indication because safer alternatives are available), ACTH and corticosteroids. An additional drug used in a very restricted indication is stiripentol, which received conditional approval from the European Medicines Agency as adjunctive therapy to valproic acid and clobazam in patients with severe myoclonic epilepsy in infancy [11].

Among drugs classified as broad spectrum, valproic acid and benzodiazepines are the only ones for which there is evidence of protective activity against virtually all seizure types, irrespective of syndromic form [12]. However, benzodiazepines are rarely used as first-line agents for chronic treatment, and valproic acid, which is often used preferentially in the management of generalized epilepsies, is regarded as the treatment of choice only when equally effective and safer alternatives are unavailable. For many second-generation drugs which are classified as broad

Table 30.1 Factors to be considered in choosing an antiepileptic drug.

Medication-related characteristics
Spectrum of efficacy against specific seizure types and syndromes
Expected magnitude of therapeutic response in the specific seizure type (syndrome)
Approved indications. Contraindications
Adverse effect profile (including teratogenicity)
Potential for interacting with other medications
Potential impact on co-morbidities
Dose escalation requirements, and ease of use in adjusting dosage
Frequency of administration
Availability of formulations (including parenteral formulations)
Cost and reimbursability
Other (mechanisms of action, monitoring requirements, quality and amount of available information)
Patient-related characteristics
Seizure type and epilepsy syndrome
Other epilepsy-related characteristics (EEG features, aetiology)
Age
Gender (including childbearing potential)
Co-morbidities
Co-medications
Response to previously administered medications (including adverse drug reactions)
Other risk factors for adverse drug reactions (including genotype)
Psychological and social setting, including personal concerns about specific side-effects

Table 30.2 Efficacy spectrum of the main antiepileptic drugs in different seizure types.

Effective or possibly effective against most seizure types	Effective against partial and secondary generalized tonic–clonic seizures	Effective against absence seizures	Effective against infantile spasms
Valproic acid	Carbamazepine[i]	Ethosuximide[l]	Vigabatrin[m]
Phenobarbital[a]	Phenytoin[i]		ACTH[n]
Primidone[a]	Gabapentin[j]		Corticosteroids[n]
Benzodiazepines[b]	Lacosamide[k]		
Lamotrigine[c]	Oxcarbazepine[i]		
Levetiracetam[d]	Pregabalin[j]		
Rufinamide[e]	Tiagabine[i]		
Topiramate[f]			
Zonisamide[g]			
Felbamate[h]			

[a] Phenobarbital and primidone are not effective against absence seizures.

[b] Benzodiazepines occasionally exacerbate tonic seizures, particularly after intravenous use in patients with Lennox–Gastaut syndrome or West syndrome.

[c] Lamotrigine may aggravate severe myoclonic epilepsy of infancy (Dravet's syndrome), and may aggravate myoclonic seizures in other syndromes. The efficacy of lamotrigine is best documented against partial and secondary generalized tonic–clonic seizures, primary generalized tonic–clonic seizures, absence seizures and drop attacks associated with the Lennox–Gastaut syndrome.

[d] Efficacy against tonic and atonic seizures has not been documented. The efficacy of levetiracetam is best documented against partial and secondary generalized tonic–clonic seizures, primary generalized tonic–clonic seizures, and myoclonic seizures.

[e] Efficacy against absence and primary generalized tonic–clonic seizures has not been documented. The efficacy of rufinamide is best documented against partial and secondary generalized tonic–clonic seizures and drop attacks associated with the Lennox–Gastaut syndrome.

[f] Efficacy against absence seizures has not been documented. The efficacy of topiramate is best documented against partial and secondary generalized tonic–clonic seizures, primary generalized tonic–clonic seizures and drop attacks associated with the Lennox–Gastaut syndrome.

[g] Efficacy against most generalized seizures types is poorly documented. The efficacy of zonisamide is best documented against partial and secondary generalized tonic–clonic seizures.

[h] Efficacy against absence, myoclonic and primary generalized tonic–clonic seizures has not been documented. The efficacy of felbamate is best documented against partial and secondary generalized tonic–clonic seizures and drop attacks associated with the Lennox–Gastaut syndrome.

[i] Carbamazepine, phenytoin and oxcarbazepine may also be efficacious against primary generalized tonic–clonic seizures. Carbamazepine, phenytoin, oxcarbazepine and tiagabine may precipitate or aggravate absence and myoclonic seizures.

[j] Gabapentin and pregabalin may precipitate or aggravate myoclonic seizures.

[k] Tentative classification. Lacosamide has not been assessed in patients with primary generalized seizures.

[l] Ethosuximide may also be efficacious against myoclonic seizures and continuous spike–waves during sleep (CSWS).

[m] Vigabatrin is also effective against partial seizures. Vigabatrin may precipitate or aggravate myoclonic seizures.

[n] ACTH and corticosteroids may also be effective in continuous spike–waves during sleep (CSWS), particularly in Landau–Kleffner syndrome.

spectrum, adequate information on potential efficacy in less-common seizure types is not available, and there seem to be specific seizure types or syndromes which are paradoxically aggravated by some of these drugs (Table 30.2) [13,14].

Because available drugs have different spectra of efficacy in relation to seizure type, a correct classification of the seizure type(s) is the most valuable single piece of information in selecting a drug for initial treatment. All efforts should also be made to establish as early as possible a correct syndromic diagnosis. In fact, if the epilepsy syndrome has been identified, drug choice can be made more rationally by taking into account additional seizure types which might occur as part of the natural history of the disorder. For example, awareness that children with childhood absence epilepsy may develop tonic–clonic seizures later in life can be used as an argument for prescribing a medication effective against both these seizure types (e.g. valproate or lamotrigine) instead of ethosuximide, which is efficacious only against absences. The epilepsy classification also provides a useful insight into the probability of a favourable response to treatment, since for any given seizure type responsiveness to treatment may vary depending on the syndromic form; for example, myoclonic jerks associated with juvenile myoclonic epilepsy are much more easily controlled than myoclonic seizures associated with the Lennox–Gastaut syndrome. Equally important, knowledge of the epilepsy syndrome allows the best prediction of the probability of the patient's achieving spontaneous remission. This is of crucial importance in determining whether drug treatment should be given for many years and possibly indefinitely, as is usually the case in juvenile myoclonic epilepsy, or whether discontinuation of therapy is feasible following an adequate interval of freedom from seizures [15].

Correct identification of seizure type and epilepsy syndrome is also very important because some antiepileptic drugs may paradoxically precipitate or aggravate seizures in patients with certain syndromes [13,14]. The most common example is the precipita-

tion of absence seizures and myoclonic jerks by carbamazepine or oxcarbazepine in patients with juvenile myoclonic epilepsy, a syndrome which is often misdiagnosed and, therefore, incorrectly treated. Carbamazepine and oxcarbazepine may precipitate myoclonic and absence (or absence-like) seizures in other types of epilepsies, particularly in patients with bursts of generalized bilateral spike-and-wave discharges in their electroencephalogram (EEG) [13,16]. Tiagabine and vigabatrin may also induce myoclonic and absence seizures, gabapentin and pregabalin may precipitate or worsen myoclonus, barbiturates may aggravate absence seizures, and lamotrigine may aggravate severe myoclonic epilepsy in infancy [13,14]. Even status epilepticus, particularly nonconvulsive status, can be precipitated by antiepileptic drugs, particularly when an agent has been chosen which is inappropriate for a specific epilepsy syndrome [17].

Magnitude of efficacy in specific seizure types

Partial seizures

Randomized comparative long-term monotherapy trials in patients with newly diagnosed partial seizures have been conducted with carbamazepine, phenytoin, valproic acid, phenobarbital, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin. Most of these trials failed to identify major differences in seizure freedom rates among the drugs being compared [2,3,6,18]. However, suggestive evidence was provided to show that valproic acid may be less efficacious than carbamazepine in reducing the frequency of complex partial seizures [19], and that gabapentin may be less efficacious than carbamazepine or lamotrigine [20,21] and phenobarbital may be less efficacious than carbamazepine and phenytoin [22] in controlling partial seizures. Whenever differences in efficacy were found, however, these were relatively modest in magnitude. It should be understood that achievement of sustained seizure freedom is dependent not only on a drug's ability to control seizures, but also on the patient being able to tolerate the administered treatment. In a few studies where appreciable differences in seizure freedom rates were identified, these were related more to differences in tolerability (e.g. number of patients withdrawing due to adverse effects) than to efficacy per se [20,23–27].

All second-generation antiepileptic drugs were also tested in placebo-controlled adjunctive therapy trials in refractory partial epilepsy, and some differences in responder rates among the various drugs emerge when results of different trials are compared [28]. However, with few exceptions [29], there are no adjunctive therapy studies evaluating active treatments head to head, and results of different trials cannot be easily compared due to specificities of the populations being assessed and differences in dosages, titration rates and study design.

Generalized seizures

Randomized controlled trials in patients with primary generalized seizures are very scarce. This is regrettable because, unlike findings for partial seizures (where no major efficacy differences seem to exist among drugs, at least in newly diagnosed patients), for some generalized epilepsy syndromes appreciable differences in magnitude of therapeutic response seem to exist between the various drugs.

Small groups of patients with primary generalized tonic–clonic seizures have been included in some monotherapy trials designed primarily to assess drug response in patients with newly diagnosed partial seizures [3]. Additionally, placebo-controlled adjunctive therapy trials in patients with refractory primary generalized tonic–clonic seizures have been completed for lamotrigine, levetiracetam and topiramate [3,30]. Overall, the data from these studies suggest that valproic acid, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, lamotrigine, levetiracetam and topiramate are all efficacious in this seizure type, although special caution is required in prescribing carbamazepine, oxcarbazepine and phenytoin in patients with syndromes potentially associated with absence and myoclonic seizures, which may be aggravated by these drugs [3]. Due to inadequate statistical power of monotherapy trials, and lack of an active control in adjunctive therapy studies, no definite conclusions on the comparative efficacy of the various drugs against primary generalized tonic–clonic seizures can be drawn from available data.

Studies in specific epilepsy syndromes are of special interest, but these have been mostly uncontrolled. A retrospective report on 962 patients with idiopathic generalized epilepsies from different clinics in the UK suggested that valproic acid may have superior efficacy to lamotrigine in these patients [31]. A more recent retrospective assessment of 103 adults with idiopathic generalized epilepsies reported similar results: remission rates were higher with valproic acid than with lamotrigine (66% versus 45%), particularly in juvenile myoclonic epilepsy (75% versus 39%) [32]. Although some patients with juvenile myoclonic epilepsy respond well to lamotrigine, there are also occasional reports of lamotrigine aggravating myoclonic seizures [33], and the overall evidence suggests that lamotrigine is not as efficacious as valproic acid in this syndrome. With respect to other generalized syndromes, randomized monotherapy trials have been reported in childhood absence epilepsy, and suggest that valproic acid has comparable efficacy to ethosuximide [12] but possibly greater efficacy than lamotrigine [34]. Finally, valproic acid was found to be the most effective drug in a large randomized open-label monotherapy trial in 716 patients, most of whom had generalized or unclassified epilepsies [27]. In patients with idiopathic generalized epilepsies, valproic acid was more effective than either lamotrigine or topiramate, and overall the data suggested that valproic acid was superior to lamotrigine in efficacy and to topiramate in tolerability. The results of this study, however, are difficult to interpret because outcome for specific epilepsy syndromes was not reported, and because the unblinded design may have biased the assessment [35].

Despite the methodological limitations of the studies conducted to date, the available evidence, including the opinion of experts, suggests that valproic acid has superior efficacy to lamotrigine and, possibly, other drugs in the treatment of some generalized epilepsy syndromes [8–10,27,32,34]. Among the newer drugs, levetiracetam shows particularly promising activity in some generalized epilepsies, including juvenile myoclonic epilepsy [36,37], but data from comparative trials are unavailable. Adequate comparative data in generalized epilepsies are not available for many

other drugs, and these gaps in knowledge should be addressed in future studies.

Adverse effect profiles

The primary goal of antiepileptic drug therapy is complete freedom from seizures without adverse effects. In some cases, particularly when seizures can be controlled with low doses, this goal can be achieved. In other cases, the best compromise should be sought between seizure protection and adverse drug effects. While the importance of seizure freedom in ensuring a good quality of life cannot be underestimated, this should not be pursued at all costs, and patients should never be made to suffer more from the adverse effects of treatment than from the manifestations of the disease [38].

No antiepileptic drug is free from adverse effects, but there are important differences in type and frequency of adverse effects caused by individual medications. Given that many different drugs are usually available to treat a given seizure type (see Table 30.2), the comparative adverse effect profile is a primary consideration in deciding which medication should be used preferentially. Some drugs, for example felbamate and vigabatrin, are associated with such a high probability of serious adverse reactions that these agents are very rarely used as first choice, except for conditions for which safer and effective alternatives are unavailable (e.g. in the case of vigabatrin, West syndrome associated with tuberous sclerosis) [39]. Other drugs have better safety records, but all are liable to produce adverse effects which interfere with quality of life [40].

The relevance of a specific adverse effect varies across patients. For example, teratogenic potential is not a relevant consideration when prescribing a drug to a man, and the risk of causing anorexia will have different implications in an underweight person compared with an obese patient, for whom this effect may even be desirable. Because of these considerations, physicians must be aware of the full range of side-effects caused by each of the drugs, together with relative frequencies and associated risk factors, and choose the medication which is least likely to impact adversely on the individual. A discussion on how specific patients' characteristics affect the risk–benefit assessment is provided later in this chapter.

Drug interaction potential

When multiple drugs are prescribed simultaneously, clinically significant adverse drug interactions may occur (Chapter 28). There are obvious advantages in using medications with little or no capability of causing or being a target for adverse drug interactions.

In specific contexts, such as the management of individuals with co-morbidities requiring concomitant drug treatment, the drug interaction potential is a particularly important consideration in choosing an antiepileptic drug. In a person with epilepsy caused by a brain tumour, for example, it is highly desirable to use preferentially an antiepileptic drug devoid of enzyme-inducing or -inhibiting properties, in order to avoid potentially fatal interactions with antineoplastic chemotherapy [41]. Similar considerations apply to HIV-infected patients, in whom the effects of antiretroviral therapy may be negated by interactions caused by enzyme-inducing drugs [42]. Elderly patients are particularly prone to suffer from co-morbidities requiring multiple drug therapy, and enzyme-inducing antiepileptic drugs may be particularly problematic in this population due to the risk of interactions with co-medications such as antianginal and antihypertensive drugs, warfarin and statins [43]. Risks also arise from interactions in which drugs used for other conditions modify the response to antiepileptic therapy.

Another context in which the interaction potential should be considered is in using combinations of antiepileptic drugs. When treatment with an antiepileptic drug combination is indicated, it makes sense to co-prescribe preferentially drugs which are least likely to result in adverse interactions. However, there are also examples of drug combinations which are apparently beneficial, and therefore may be used advantageously. These issues are discussed in detail in Chapters 9 and 28.

The interaction potential of an antiepileptic drug is of relevance also when prescribing to patients not currently taking other medications. Because antiepileptic drugs are often taken for many years, sometimes for a lifetime, it is likely that in the future many patients will need to take other medications, for example a hormonal contraceptive, a chemotherapeutic agent or a cardiovascular drug. The efficacy and safety of such medications may be complicated by pre-existing therapy with an antiepileptic drug characterized by high interaction potential.

Impact on co-morbidities

The potential interactions between antiepileptic drugs and co-morbidities are complex. Some antiepileptic drugs have a precipitating or aggravating effect on specific co-morbidities, which may represent an absolute or relative contraindication to their use in affected patients. However, there are also co-morbid conditions which are influenced beneficially by specific antiepileptic drugs. Examples of co-morbidities influencing drug selection are given below in this chapter in the section discussing the importance of patient-related factors.

Other medication-related factors

Mechanisms of action

It may sound heretical to state that knowledge of mechanisms of drug action has little relevance for selecting a drug in the clinic, but this is the way antiepileptic drugs are mostly prescribed at present. In fact, our understanding of the pathophysiology of the epilepsies and of the modes of action of individual drugs is still too fragmentary to allow mechanism-driven rational drug selection. Although primary modes of actions have been described for most antiepileptic drugs, additional mechanisms have not been identified and their relative contribution to clinical effects in an individual patient is poorly understood. To give one example, lamotrigine is often referred to as a selective blocker of voltage-dependent sodium channels, but it has also been found

to inhibit N-type, L-type and P-type calcium channels, to increase brain γ-aminobutyric acid (GABA) levels, to increase potassium conductance, to stimulate taurine-mediated neurotransmission and to act as an antagonist or negative modulator at the 5-hydroxytryptamine 1A ($5HT_{1A}$) receptor [44]. How each of these actions could account for therapeutic and adverse effects is unclear.

While these limitations should be understood, there are situations in which knowledge of modes of action need to be considered in choosing a medication. In a patient who has shown a paradoxical aggravation of seizures on carbamazepine, for example, it would be sensible to avoid, if possible, medications such as oxcarbazepine and phenytoin, which have modes of actions similar to carbamazepine. Likewise, in patients with refractory seizures who require multiple drug therapy, the suggestion has been made that combinations of drugs possessing different modes of action should produce better responses than combinations of drugs acting through a similar mechanism, even though clinical evidence in support of this hypothesis is limited and not always consistent [45].

In time, research on the relationship between specific modes of action and clinical response in well-defined epilepsy syndromes could yield important clues for rational treatment; for example, it might be possible in the future to determine which drug produces the best response in a patient whose epilepsy is caused by a specific channelopathy, a mutation in an excitatory amino acid receptor, or an impairment in central GABAergic transmission. In fact, evidence is starting to emerge that, in certain conditions, knowledge of modes of drug action can aid in predicting responses to treatment. For example, a drug-induced selective increase in GABA concentration in the synaptic space, as produced by agents such as tiagabine and vigabatrin, seems to predict efficacy against partial seizures but also, potentially, aggravation of absence and myoclonic seizures [13].

Availability of appropriate formulations

When an immediate effect is required, such as in the management of status epilepticus or acute repetitive seizures, treatment choices are restricted to medications which have a fast onset of action, can be safely loaded in an emergency setting, and are available in a rapidly absorbed formulation. Formulations suitable for intravenous use are advantageous in most cases, but alternative formulations which ensure rapid absorption by other routes, such as the buccal, rectal or intranasal route, may be appropriate in selected situations [46].

Patients stabilized on oral treatment may be temporarily unable to take their regular medicines, for example after abdominal surgery or during an illness causing repeated vomiting. Parenteral formulations which can be used to provide therapeutic cover in these situations are not available for all drugs, and in some cases availability of a parenteral formulation should be taken into account in deciding which drug should be preferentially prescribed.

In some patients, particularly children less than 5 years of age, intake of tablets and capsules may be problematic, and other dosage forms such as solutions, suspensions, powders or granules provide useful alternatives [47]. Some liquid formulations are associated with rapid gastrointestinal absorption which, in turn, may lead to prominent fluctuations in plasma drug concentrations and increased risk of adverse effects at the time of peak, or seizure breakthrough at the time of trough. Some paediatric formulations, additionally, contain tooth-damaging ingredients such as sucrose, or have an unsatisfactory palatability, which may adversely affect compliance. Indeed, optimal paediatric formulations are not available for many antiepileptic drugs, a situation which restricts treatment choices in the younger age groups.

For certain drugs, modified-release products are available, which allow less frequent dosing, with beneficial effects on convenience and compliance. Some of these formulations also improve efficacy and tolerability by minimizing fluctuations in plasma drug levels during the dosing interval [48].

Dose escalation requirements

As discussed in Chapter 9, drugs such as phenytoin, levetiracetam, gabapentin and pregabalin can be up-titrated relatively rapidly to the fully efficacious dose range, while others, particularly primidone, lamotrigine, topiramate, zonisamide and tiagabine, require a slow dose escalation to minimize the risk of adverse effects. Whenever a rapid onset of action is required (for example, in patients with frequent seizures, or in those who developed an idiosyncratic reaction on their previous therapy and need to be switched rapidly to an alternative agent), a medication which can be up-titrated rapidly has obvious advantages [47].

There are also advantages in preferring drugs for which dose individualization is comparatively easy. Adjusting the dose of phenytoin, in particular, can be difficult due to Michaelis–Menten pharmacokinetics and large inter-patient variability in dose requirements.

Monitoring requirements

Some drugs require special monitoring procedures to ensure optimal efficacy and to minimize the risk of adverse effects. For example, individualizing phenytoin dosage can be difficult without measuring its plasma concentration [49], which may argue against the preferential use of this drug in settings where a therapeutic drug monitoring service is unavailable. Likewise, therapy with felbamate requires repeated blood chemistry and haematology tests, and this drug should not be prescribed if compliance with safety monitoring tests cannot be guaranteed.

Cost of treatment

Over 40% of the world's population live in a country where the per capita annual gross national product barely suffices to buy a year's supply of carbamazepine or valproic acid for one or two patients. Therefore, it is no surprise that, in many settings, cost is a major consideration not only in deciding which drug to use, but also in determining whether drug treatment is affordable at all. This problem is aggravated by the fact that in many developing countries the price of antiepileptic drugs is considerably higher than in the industrialized world. For most patients in developing countries, only phenobarbital is available at prices affordable by the general population, and many of the newer drugs may not be available at all [50].

Cost is an important issue also for affluent societies, particularly in view of the fact that recently licensed drugs are far more expensive than older agents. In some countries, reimbursement of

Table 30.3 Ideal properties for an easy-to-use antiepileptic drug.

Broad spectrum of activity against all seizure types
High efficacy
Good tolerability
No risk of allergic or idiosyncratic reactions (including teratogenicity)
Low interaction potential
Low variability in dosage requirements
Favourable pharmacokinetics (linear kinetics, half-life compatible with once- or twice-daily dosing)
Fast and easy dose escalation rate
No tolerance to antiepileptic effects
No withdrawal seizures
No need for intensive laboratory monitoring
Availability of convenient formulations (including convenient paediatric dosage forms and a parenteral formulation)
Low cost

medication costs by health services or insurance schemes is only applicable to specific drugs (or formulations), specific indications or patients within predefined income limits. The cost of many antiepileptic medications has decreased in recent years due to the introduction of generic products. Advantages and concerns with the use of these products are discussed in Chapter 9.

Ease of use

Not all antiepileptic drugs are equally easy to use, a consideration which impacts on drug selection. Ease of use encompasses many properties discussed above in this chapter: in particular, a broad efficacy spectrum against many seizure types, a good safety and tolerability profile, a low interaction potential, feasibility of once- or twice-daily dosing, availability of convenient formulations, and rapid and simple schemes for dose titration and individualization all contribute positively to ease of use (Table 30.3).

Old or new drugs?

When the cost of medication is not a major constraint, drug selection should be based primarily on the expected benefit to risk balance in the individual patient. When this is taken into account, the increasing use of newer drugs in the last decade may be justified by the improved tolerability profile and the lower interaction potential which characterize some of these agents. However, evidence concerning merits and demerits of individual medications should be evaluated critically. In some randomized trials which compared newer and older generation drugs, results may have been biased by specificities in the study design which discriminated against the older drug [51]. For example, when carbamazepine was used as comparator, its target dosage was sometimes higher than necessary, and an immediate-release formulation was almost invariably used despite evidence that sustained-release preparations are associated with superior tolerability [52]. When assessing risks associated with specific medications, it should also be remembered that the latency between the introduction of a drug in the market and the discovery of potentially important adverse effects can be long. It took 10 years since marketing to identify the hepatic toxicity of valproic acid, and 8 years to discover vigabatrin-induced visual field loss [39].

Approved versus off-label use

As a general rule, medications should be used according to indications approved by regulatory authorities. The approval of a specific indication is dependent on submission of adequate efficacy and safety data to regulatory agencies. Given the heterogeneity of seizure disorders, however, certain seizure types or syndromes are rarely investigated in regulatory trials. As a result, many antiepileptic drugs are not formally approved for some indications or for specific age groups, despite evidence of clinical usefulness in the same conditions from non-regulatory studies or clinical experience. The situation is further complicated by the fact that regulatory standards for approval have changed over the years, resulting in discrepancies in the quality of supportive evidence between older and newer generation drugs. Approved indications also vary from country to country; for example, many drugs which have monotherapy approval in Europe are not approved for monotherapy use in the USA [4]. Other concerns relate to the appropriateness of dose titration schemes and dosing schedules approved by regulatory authorities. These reproduce dosing procedures in regulatory trials and do not necessarily reflect optimal dosing schemes, which are mostly established during post-marketing experience [47].

In view of the above considerations, off-label prescribing is justifiable in selected situations, and in many countries there is a legal framework for this. In the USA, for example, the statutory authority of the Food and Drug Administration is focused on pre-marketing testing, and safe and effective prescribing is left to the physician's responsibility [53]. Off-label prescribing is widespread: in a recent survey of office-based physicians in the USA, 46% of all prescriptions of anticonvulsants were found to be off label (including, presumably, also indications outside epilepsy) and, remarkably, 83% of these were backed by either little or no published scientific evidence [54]. Off-label use is especially prevalent in uncommon epilepsy syndromes, particularly in infants and young children, for which few or no drugs are formally approved. Physicians prescribing off label, however, should be aware of legal liability issues, and must ensure that their decisions are backed by the best medical evidence available. In some countries, the cost of drugs prescribed off label is not reimbursed by the national health system or insurance organizations, a situation which can impact on drug selection.

The importance of patient-related factors

Since rational prescribing requires finding the best match between the properties of a drug and the characteristics of the patient, careful assessment of individual features plays a crucial role in drug selection. Some of these features relate to demographics, others to psychosocial aspects, and others to the characteristics of epilepsy, associated conditions and co-medications. In considering the importance of these factors, the patient's informed opinion should be taken into consideration.

Seizure types and epilepsy syndrome

As discussed earlier in this chapter, antiepileptic drugs differ in their spectrum of efficacy against different seizure types. There-

fore, correct identification of seizure type(s) and, whenever possible, epilepsy syndrome is very important for drug selection. Whenever a diagnosis of epilepsy is established but the precise type of seizures or syndrome is uncertain, the probability of achieving seizure control is enhanced by prescribing a drug with a broad efficacy spectrum.

Aetiology of epilepsy

Defining the aetiology of epilepsy is important to identify conditions which may require specific treatments, e.g. surgery for a brain tumour. Information on aetiology is also important to establish the epilepsy syndrome, and to formulate a prognosis. In a hospital-based observational survey of 2200 patients, 1-year remission rates on drug therapy were 82% in patients with idiopathic generalized epilepsy, 45% in those with cryptogenic partial epilepsy, 35% in those with symptomatic partial epilepsy, and only 11% in those with partial epilepsy associated with hippocampal sclerosis [55]. Patients with hippocampal sclerosis and another lesion had only 3% probability of achieving seizure freedom. In the same study, patients with temporal lobe epilepsy responded more poorly to treatment than patients with extratemporal foci. Information on aetiology is also important for early identification of candidates to epilepsy surgery.

In most epilepsy syndromes, information about aetiology is of little value in predicting which specific drug will produce the best clinical response. However, this may change in the future as our understanding of the pathophysiology of the epilepsies and mechanisms of drug action will progressively improve. One important example of how aetiological information can be relevant for drug selection is provided by evidence that symptomatic infantile spasms secondary to tuberous sclerosis respond better to vigabatrin than to hydrocortisone [56], whereas cryptogenic spasms or symptomatic spasms secondary to other aetiologies seem to respond better to ACTH or steroids than to vigabatrin [57,58]. The superiority of ACTH or steroids in controlling spasms not associated with tuberous sclerosis, however, may be limited to the initial weeks of treatment, even though there is evidence that better initial control of spasms by hormone treatment in infants without identified underlying aetiology may be associated with improved developmental outcome [59].

Evidence for a preferential response to a specific drug in relation to epilepsy aetiology in other syndromes is unsubstantial, although there are anecdotal reports of potentially useful associations. For example, in preliminary studies, seizures associated with glial tumours have been found to respond relatively well to tiagabine [60].

Electroencephalographic features

Like aetiological factors, EEG features are important for differential diagnosis and for prognosis, and therefore they have an indirect influence on the process leading to drug selection. Whether the EEG features may predict differential responses to specific antiepileptic drugs in a given epilepsy syndrome has been little investigated, but some evidence suggests that this may well be the case. Patients with a history of generalized spike-and-wave paroxysms in the EEG, for example, may be at special risk of developing absence seizures and even non-convulsive status when treated with carbamazepine [13].

Genotypes

Variation in genes controlling drug-metabolizing enzymes and/or the expression of voltage-gated sodium channels has been reported to influence dosing requirements for phenytoin and carbamazepine [61]. At present, however, no genetic test is available that could be used to predict which drug will prove the most efficacious in an individual patient. With expanding pharmacogenomic knowledge, this situation may well change in the future.

The mechanisms responsible for many adverse drug reactions are also under genetic modulation, and genetic testing is already being used to identify subjects at risk [61,62]. For antiepileptic drugs, the most notable example is the determination of the human leucocyte antigen (HLA) allele B*1502 to predict the risk of serious skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) in patients with ancestry from many areas of Asia, including South Asian Indians [63–65]. The absolute risk of serious skin reactions to carbamazepine is estimated at about 5–8% in HLA-B*1502 carriers, and carbamazepine should not be prescribed to subjects with this genotype unless the expected benefits clearly outweigh the risk. In the same subjects, it is advisable to also avoid other drugs potentially associated with serious skin reactions (particularly phenytoin, for which the risk of serious cutaneous reactions also appears to be linked to the HLA-B*1502 allele), provided that alternative therapies are equally acceptable. Based on these data, the Food and Drug Administration has made testing for HLA-B*1502 mandatory before prescribing carbamazepine to patients from Asian origin [61]. HLA genotyping is of little value in identifying sbjects at risk for carbamazepine-induced serious skin reactions in whites, probably due to the low frequency of the HLA-B*1502 allele in this ethnic group [66].

Age and gender

The toxicity of many antiepileptic drugs is age dependent [62,67]. For example, the incidence of valproic acid-induced liver toxicity in children below 2 years of age who are also receiving concomitant enzyme-inducing anticonvulsants is in the range of 1:600 to 1:800, compared with less than 1:20 000 in adults [12,39]. The incidence of lamotrigine-induced serious skin rashes, including Stevens–Johnson syndrome, has also been found to be greater in children than in adults (about 1:100 versus 1:1000, respectively) [63], even though the magnitude of the risk in children may have been overestimated in early studies due to use of higher initial doses and faster titration rates than currently recommended [68]. While benzodiazepines and barbiturates may affect adversely cognitive function in any age group, children are more likely to develop hyperactivity and other behavioural disturbances, and overall they tolerate these drugs poorly compared with adults [40]. Phenytoin is known to cause acne, hirsutism, gum hyperplasia and coarsening of facial features, particularly when taken during childhood, and it is preferably avoided in children and young females when appropriate alternative treatments are available. At the other extreme of age, the elderly also show an increased sensitivity to the adverse effects of many drugs. In particular, there is evidence that carbamazepine may be tolerated

relatively poorly by elderly patients [69,70], even though tolerability problems seem to be considerably reduced when the sustained-release formulation is used [52]. Lamotrigine seems to be fairly well tolerated in the elderly [52,69,70], and therefore it represents a valuable choice in these patients. The elderly are also prone to receive other drugs for the treatment of unrelated conditions, and in order to prevent potentially hazardous interactions it is generally preferable in this population to avoid enzyme-inducing drugs such as phenytoin, carbamazepine and barbiturates [71]. Drug choices in different age groups are discussed in Chapters 13, 14 and 16.

Gender also impacts on drug selection. Some antiepileptic drugs influence endocrine and sexual functions in a gender-specific manner, and therefore they have different tolerability profiles in males and females. There is increasing recognition that some antiepileptic drugs adversely affect sexual function in men [72]. The range of gender-related effects, however, is broader in females. Adverse effects of special relevance to women, such as osteoporosis or hirsutism, and potential interactions with hormonal contraceptives [43] need to be considered when selecting an antiepileptic drug for a female patient. Other major issues relate to the effects of pregnancy on drug disposition and the adverse effects of drugs on fetal development [73]. Criteria for drug selection in women of childbearing potential are discussed in Chapter 25. It should be noted that gender-related drug effects may extend beyond the endocrine and the reproductive system. For example, the frequency of skin rashes induced by a variety of antiepileptic drugs has been found to be twice as high in women as in men [74].

Co-morbidities and co-medications

Co-morbidities are a major consideration in drug selection. Some disorders may predispose to adverse reactions to specific drugs, and may even contraindicate the use of these medications in affected patients. For example, the risk of valproic acid-induced liver toxicity is greatly increased in patients with some inborn metabolic disorders, such as urea cycle defects, and valproic acid should not be used in these patients [62]. Some drugs have the potential for aggravating co-morbidity; for example, acute intermittent porphyria can be aggravated by most antiepileptic drugs, but there are agents, in particular gabapentin and levetiracetam, which can be safely prescribed in these patients [75]. Drugs which are extensively cleared by hepatic metabolism, and drugs which are potentially hepatotoxic, should be preferably avoided in patients with liver disease. Many other co-morbid conditions may be aggravated by specific antiepileptic drugs, or they may themselves predispose to adverse drug reactions [62,75]. Interactions between co-morbidity and antiseizure medications can be particularly complex in patients with learning disabilities and in those with a history of behavioural or mood disorders, and choice of treatment in these patients must be individualized carefully (Chapters 17 and 21).

Some antiepileptic drugs influence favourably specific co-morbidities [76], an observation which can be usefully exploited. For example, carbamazepine can be a rational choice for patients with focal epilepsy and trigeminal neuralgia, gabapentin or pregabalin should be considered for patients with co-morbid neuropathic pain, and valproic acid or topiramate for patients with co-morbid migraine. Other examples of medications efficacious in co-morbidities include valproic acid and carbamazepine for bipolar disorder, pregabalin for generalized anxiety disorder, lamotrigine for bipolar depression, and primidone or topiramate for essential tremor [76,77].

Co-morbidities often require treatment with additional medications. In co-morbid conditions which require (or are likely to require in the future) use of narrow therapeutic index drugs such as antineoplastic agents, anticoagulants, immunosuppressants and many anti-infectious and cardiovascular drugs, there are strong reasons for prescribing preferentially antiepileptic drugs which are unlikely to be involved in drug–drug interactions [43].

Other patient-related factors

A history of adverse reactions to previous medications is an important factor to be considered in drug selection. For example, the risk of a skin rash after starting an antiepileptic medication is five times greater among patients with a history of a rash on another antiepileptic drug than in those without [78]. Cross-reactivity for immune-mediated adverse drug reactions is particularly common with compounds sharing a similar structure: in a retrospective study of cross-reactivity among aromatic anticonvulsants, 10 of 17 patients who had a rash from phenytoin also had a rash from carbamazepine, and 10 of 25 patients who had a rash from carbamazepine also had a rash from phenytoin [79]. In these patients, it is preferable to use drugs which are structurally unrelated and have a low potential for causing serious skin rashes, such as valproic acid, levetiracetam, gabapentin and benzodiazepines.

Other factors to be considered include the patient's profession, and his or her attitude towards the risk of seizure recurrence or towards adverse effects known to be associated with specific treatments. Prescription of a medication known to cause subtle cognitive effects, for example, may have a different impact in a young student compared with a middle-aged rural worker. Drugs requiring complex dosing schemes should especially be avoided in individuals who are expected to have difficulties with compliance.

Conclusions

Each of the existing antiepileptic drugs differs fully or partially from others in clinically relevant properties such as spectrum of efficacy, contraindications, adverse effect profile, pharmacokinetic characteristics, dose optimization requirements, range of available formulations, drug–drug interaction potential and impact on co-morbid conditions. Rational drug selection should take into account each of these factors, and assess how the specificities of each medication are expected to match with the characteristics of each individual. This assessment requires not only knowledge of the properties of the various drugs, but also careful ascertaining of medical history, clinical symptoms and signs, and the patient's emotions and opinions. Personalization of treatment should not be restricted to the choice of an antiepileptic drug, but should extend to individualization of dosage, close follow-up and monitoring of clinical response, and the provision of other

measures, including psychological support, which are necessary to address each person's unique needs.

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31 Acetazolamide

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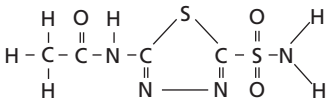

Primary indication	Adjunctive therapy of partial or generalized seizures (including absence) and myoclonus. Also Lennox–Gastaut syndrome. Intermittent therapy in catamenial epilepsy
Usual preparation	Tablets: 250 mg
Usual dosage	250–750 mg/day
Dosing frequency	2–3 times daily
Significant drug interactions	Salicylate and digitalis can increase acetazolamide levels. Acetazolamide can reduce primidone and carbamazepine levels
Serum level monitoring	Not routinely done
Reference range	Not applicable
Common/important adverse effects	Nausea, vomiting, diarrhoea, loss of appetite, weight loss, dysgeusia, paraesthesiae, headache, dizziness, flushing, drowsiness, fatigue, irritability, hyperventilation, depression, thirst, loss of libido, metabolic acidosis and electrolyte changes. Risk of renal calculi. Rarely, severe haematological, dermatological or systemic idiosyncratic reactions
Main advantages	Useful adjunctive therapy and also as intermittent therapy, usually well tolerated
Main disadvantages	Risk of idiosyncratic reactions. High incidence of tolerance
Mechanism of action	Carbonic anhydrase inhibition
Oral bioavailability	>90%
Time to peak levels	1–3 h
Metabolism and excretion	No metabolism. Eliminated by the kidney (20% by glomerular filtration and 80% by renal tubular excretion)
Volume of distribution	0.2 L/kg
Elimination half-life	10–15 h
Plasma clearance	–
Protein binding	90–95%
Active metabolites	None
Comment	Useful broad-spectrum drug for adjunctive therapy of resistant epilepsy. Use limited by tolerance and risk of idiosyncratic reactions

Introduction

Acetazolamide (Diamox) is a sulphonamide derivative which shares with other structurally related agents the ability to inhibit carbonic anhydrase, an effect that is considered to mediate its antiepileptic activity [1]. Carbonic anhydrase is a widely distributed enzyme with many different physiological functions [2,3]. Cohen and Cobb [4] were the first to identify antiepileptic activity in this chemical class. They found that azosulphamide, a vital dye, has an anticonvulsant action in experimental animals as well as in humans. They speculated that the effect produced by this drug resulted from inhibition of carbonic anhydrase,

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Table 31.1 Non-epilepsy indications and uses of acetazolamide.

Glaucoma
Diuresis
Pseudotumory cerebri
Paroxysmal ataxia
Paroxysmal dystonia
Periodic paralysis
Prevention of mountain sickness

causing acid–base changes that are manifested by metabolic acidosis.

Acetazolamide was first synthesized by Roblin and Clapp [5]. The acidifying effect of acetazolamide led Bergstrom *et al*. [6] to use it for the treatment of epilepsy, although it was later shown [2,7,8] that its anticonvulsant effect is independent of systemic metabolic acidosis and correlates directly with the degree of inhibition of carbonic anhydrase in the brain. Because carbonic anhydrase is found in many tissues other than brain and because it serves numerous functions, inhibition of carbonic anhydrase by acetazolamide is associated with diverse uses (Table 31.1). Acetazolamide inhibits the secretion of aqueous humour by the ciliary process of the eye and decreases intraocular pressure, an effect that is exploited in the treatment of glaucoma [9]. Acetazolamide has been found effective in promoting diuresis [10], and in reducing cerebrospinal fluid (CSF) pressure, for instance in pseudotumour cerebri [11]. It has also been reported to be useful in the management of paroxysmal periodic ataxia [12], paroxysmal dystonia described with central demyelinating disease [13], valproate-induced tremor [14], hypokalaemic and hyperkalaemic periodic paralysis [15] and myotonia [16]. It is also used for the prevention or amelioration of symptoms associated with acute mountain sickness [17] (Table 31.1).

The efficacy of acetazolamide in patients with epilepsy was reported mainly in the 1950s [8,18–30] and only occasional studies were performed several decades later [31–35]. However, because no adequately controlled clinical trials have been conducted, the efficacy of this drug in different seizure types and syndromes, and specifications for appropriate management, are neither well established nor well documented.

Chemistry

Acetazolamide corresponds to 2-acetylamido-1,3,4-thiadiazole–5 sulphonamide. It is a white-yellowish crystalline powder, poorly soluble in water and readily soluble in alkaline solutions. Its molecular weight is 222 and its pK_a is 7.4.

Mechanism of action and activity in animal models

The anticonvulsant effect of acetazolamide is mediated by inhibition of carbonic anhydrase [7,8], which catalyses the formation of H_2CO_3 in the equilibrium reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$. The secondary reaction $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$ is instantaneous, causing spontaneous dissociation of the carbonic acid. Carbonic anhydrase is present in high concentration in erythrocytes, gastric mucosa, the renal cortex, and in the lens and retina [2,3]. It is located in the brain in the cytoplasm and the membrane of glial cells and in the choroid plexus [36–38], as well as in myelin derived from oligodendrocytes [38,39]. Oligodendrocytes have higher carbonic anhydrase activity than astrocytes [39]. Carbonic anhydrase in the brain has an important role in the neurone–glia metabolic relationship. It is involved in regulating ionic balance throughout the brain [40]. Specifically, it catalyses the hydration of CO_2 that is generated during neuronal activity. The products of this reaction are hydrogen and bicarbonate ions that are exchanged across the glial membrane for sodium and chloride, respectively [41]. Carbonic anhydrase is involved in the maintenance of Cl^- and K^+ concentrations in glial cells [42].

Mann and Keilin [1] were the first to discover that sulphanilamide had a specific and powerful inhibiting effect on the activity of carbonic anhydrase. A study of other sulphonamides revealed that acetazolamide was several hundred times more potent than sulphanilamide as an inhibitor of carbonic anhydrase [5].

Acetazolamide shows wide-spectrum anticonvulsant activity in several animal models. It exerts a depressant action in the spinal cord, which is highly selective for the monosynaptic pathway [43]. Acetazolamide abolishes the tonic extensor component of maximal electroshock convulsions [7,43,44], thereby raising seizure threshold [44]. It also protects against seizures caused by pentylenetetrazol [43] or CO_2 withdrawal [45], as well as against audiogenic seizures [46]. The anticonvulsant activity of acetazolamide was originally thought to be a result of its acidifying effects, caused by inhibition of renal carbonic anhydrase – apparently resembling the effects of the ketogenic diet. However, by using the maximal electroshock seizure model in mice, Millichap *et al*. [7] demonstrated that acetazolamide has an anticonvulsant effect which is independent of its action on the kidney and which correlates directly with the degree of inhibition of carbonic anhydrase in the brain. Other investigators [8,47] confirmed that the anticonvulsant action of carbonic anhydrase inhibitors is correlated with inhibition of brain carbonic anhydrase and independent of inhibition of the erythrocyte enzyme or diuresis. In the brain, inhibition of glial carbonic anhydrase reduces the conversion of neuronally derived CO_2 to HCO_3, whereupon neuronal CO_2 accumulates and glial pH is lowered [7,8,47,48]. The anticonvulsant action of carbonic anhydrase inhibitors at neuronal level may be related to the demonstrated effects of CO_2 on nerve sensitivity and propagation of nerve impulses [2,49]. Both CO_2 and acetazolamide increase the electroshock seizure threshold and abolish the tonic extensor phase of seizures induced by maximal electroshock [43,49]. In addition, the effects of acetazolamide on maximal electroshock seizures and on spinal cord synaptic transmission are potentiated by CO_2 [46]. The similarities between the anticonvulsant effects of CO_2 and acetazolamide suggest that the influence of carbonic anhydrase on seizure activity is mediated through the CO_2 buffering system [48,49]. Following administration of acetazolamide and inhibition of carbonic anhydrase, analysis of both glial cells and myelin shows elevation of CO_2 in the extracellular space surrounding the neuronal cells and the axons where it could inhibit spread of neuronal activity or stabilize the axonal membrane [49]. Similar to CO_2, acetazolamide also increases γ-aminobutyric acid (GABA) levels in the brain [43], which may account for some of its anticonvulsant effects.

Pharmacokinetics

Absorption

Since acetazolamide is a weak acid, its absorption is affected by factors such as pH and lipid and water solubility [50]. After oral doses of 5–10 mg/kg daily, acetazolamide is completely absorbed from the gastrointestinal tract [51,52], whereas higher doses may be incompletely absorbed [52]. At commonly used doses, oral bioavailability is above 90%. Absorption begins in the stomach but occurs mainly in the duodenum and upper jejunum where the surface area is larger. Peak plasma concentrations of around 10–18 μg/mL were reached 1–3 h after oral ingestion of a single 250-mg dose, while the peak erythrocyte concentration was reached 1 h later and was in the order of 13–19 μg/mL [53]. Following administration of single oral 500-mg doses as a sustained-release (SR) formulation, peak plasma concentrations were obtained 3.5 h after dosing and a level of about 10 μg/mL was maintained for 10 h [54]. Oral administration of an SR form causes less fluctuation in drug plasma concentrations [55].

Distribution

Acetazolamide is extensively bound to plasma proteins (fraction bound 90–95%), and this binding is concentration dependent and reduced in the elderly [51,56]. The free (unbound) fraction increases with increasing plasma concentration. Half of the free concentration is in unionized form, and it is this component that penetrates into tissues and causes inhibition of carbonic anhydrase [50]. When binding to tissue carbonic anhydrase, acetazolamide forms an enzyme–inhibitor (EI) complex and, after 24 h, almost all of the drug is present in the various tissues in this form, most of it being found in the erythrocytes, kidney and stomach.

The plasma half-life of acetazolamide has two components. The fast component represents the distribution of the unbound diffusible drug throughout the body and is rather short (about 2 h) [53]. The EI complex has a slow dissociation constant and the drug is released slowly from tissues and is then excreted unchanged in the urine. The elimination phase is characterized by a half-life of around 10–15 h [50].

The volume of distribution of acetazolamide in humans based on total plasma concentration is 0.2 L/kg, and it is 1.8 L/kg when calculated from the free level in the plasma [50]. Following distribution, the free concentration of acetazolamide in tissues is higher than in plasma, and highest in erythrocytes. Acetazolamide penetrates slowly into the brain, where its concentration is lower than in plasma, but higher than in CSF. The concentration of acetazolamide in CSF increases more than the free concentration in plasma at high doses of the drug. This effect suggests that acetazolamide is actively transported out of the CSF and that saturation of the transport system at high concentrations results in increased drug levels in the CSF [50].

Elimination

As discussed above, the elimination half-life of acetazolamide is 10–15 h. The drug does not undergo metabolic transformation and it is excreted unchanged in urine, 20% by glomerular filtration and 80% by renal tubular excretion [2,51,52]. Renal elimination is restricted to the unbound fraction in plasma [56]. Most of a single oral dose is recovered in the urine in 24 h [52]. Elderly patients have a higher unbound fraction and a reduced clearance of unbound drug.

Drug interactions

Acetazolamide is not metabolized and therefore induction or inhibition of drug-metabolizing enzymes has no influence on plasma acetazolamide levels.

Because acetazolamide reduces the production and flow rate of CSF, it may theoretically increase the concentration of other centrally acting drugs. On the other hand, drugs that inhibit CSF production, such as digitalis, may increase the concentration of acetazolamide in the CSF and brain [50]. By alkalinizing urine, acetazolamide would be expected to increase the renal clearance of acidic drugs and to reduce the renal clearance of basic drugs.

Salicylate appears to competitively inhibit the plasma protein binding of acetazolamide and to simultaneously inhibit its secretion by renal tubules [57]. Increased free drug concentration may have been responsible for symptoms of toxicity in two elderly patients with glaucoma who were treated with aspirin and acetazolamide and developed symptoms of lethargy and confusion with metabolic acidosis [57]. In another study in three patients, acetazolamide was reported to interfere with primidone absorption, causing decreased levels of primidone in the plasma and urine [58]. Acetazolamide has been reported to increase the serum concentration of carbamazepine in children when given concomitantly [31]. The mechanism of this interaction remains obscure.

Serum level monitoring

No adequate data on the usefulness of serum drug level monitoring are available.

Efficacy

General overview of results of clinical trials

In 1952, Bergstrom *et al*. [6] were the first to use acetazolamide in the treatment of epilepsy. Given that the drug reduces acid excretion by the kidney, causing metabolic acidosis, the authors speculated that it might be similarly effective in patients with epilepsy as the use of a ketogenic diet. They administered acetazolamide 10–30 mg/kg daily as adjunctive therapy to 42 patients with intractable epilepsy (neither their ages nor type of seizures were mentioned). A decrease in seizure frequency by 50–100% was achieved in 8 of the 42 (20%) patients, and the condition did not worsen in any of the patients.

In subsequent studies, selection of patients, definition of seizure type, treatment procedures and follow-up periods have varied widely and results are therefore difficult to compare [6,18–35,50,59,60] (Table 31.2).

Most studies reported acetazolamide to be effective against refractory generalized and partial seizures. However, these reports were compiled prior to the adoption of the International Classification of Seizures and Epilepsies, and only a few studies classified seizures according to the present classification. Golla and

Table 31.2 Clinical trials with acetazolamide.

Reference	No. of evaluated pts	Age range	Diagnosis/seizure type	Therapeutic regimen	Follow-up period	Seizure decrease – number (%) of pts			Adverse effects – number (%) of pts
						90–100%	>50%	n/s	
Bergstrom *et al.* [6]	42		Refractory epilepsy	10–30 mg/kg	Not mentioned	4 (10)	4 (10)	34 (80)	Fatigue, flushing, polydipsia, hyperpnoea, paraesthesiae, headache
Lombroso *et al.* [18]	126	82 pts <12 y 24 pts 12–19 y 20 pts >20 y	All seizures: 29 petit mal 41 petit mal and other seizures 56 non-petit mal	8–30 mg/kg 250–1500 mg/day 63 pts on mono 63 pts on add-on	3–36 m	46 (36) 8 (27) 19 (46) 20 (36)	22 (17) 4 (14) 8 (20) 9 (16)	58 (46) 17 (59 14 (34) 27 (48)	Drowsiness 19 (15), anorexia 17 (13), irritability 11 (9), rash, tingling, dizziness, enuresis, vomiting, ataxia, hyperpnoea in 2–5 (2–4)
Merlis [19]	47	19–64 y	Chronic epilepsy with psychosis	500–1000 mg/day 13 pts on mono 34 pts on add-on	11 m	29 (62)	6 (13)	12 (25)	Transient flushing, headache, fatigue in 4 (9)
Millichap [20]	14	6 m to 11 y	All seizures: 6 generalized 7 focal 1 myoclonic jerks only	18–36 mg/kg 750 mg/day Double-blind placebo-controlled 2 pts on mono	5–26 w		5 (36)		Anorexia 5 (36), polyuria 5 (36), nocturnal enuresis 4 (28), drowsiness 3 (21), vomiting 1 (7), diarrhoea 1 (7)
Ansell and Clarke [21]	26	12–38 y	All seizures: 23 idiopathic generalized 3 symptomatic	3–14 mg/kg 9 pts on mono 17 pts on add-on	1.5–20 m	8 (31)	6 (23)	12 (46)	5 (19) paraesthesiae, 4 (15) drowsiness, 1 (4) depression
Livingston [22]	58	8 m to 14 y	25 major motor 18 minor motor 15 petit mal	≤1250 mg/day 14 pts on mono 44 pts on add-on	2–6 m	Temporary decrease in the frequency of seizures in a few pts		25 (100) 18 (100) 15 (100)	
Golla and Hodge [23]	78	6–35 y	Petit mal	250 mg add-on	3–10 m	76 (97)		2 (3)	Transient tingling of hands and feet, and somnolence
Minde *et al.* [24]	20	5–36 y	Symptomatic	12 mg/kg add-on mono	50 days 50 days	12 (60) No significant improvement in pts on mono	5 (25)	3 (15)	Fatigue 3 (15), diarrhoea 2 (10), excitement 1 (5)
Wada *et al.* [25]	21	10 m to 40 y	Convulsive group, petit mal group, psychomotor group	250–1000 mg/day 5 pts on mono 16 pts on add-on	8–85 days	6 (29)	6 (29)	9 (42)	Increased diuresis 6 (28)
Baird and Borofsky [26]	16	Children	Infantile spasms	1000 mg/day mono	1–3 m			16 (100)	
Holowach and Thurston [27]	56	3 m to 16 y	All seizures: 4 grand mal 14 petit mal 20 focal (frontal and temporal) 11 massive myoclonic 1 tonic 6 mixed	250–1000 mg/day add-on	2–20 m	35 (63) 3 (75) 9 (64) 12 (60) 5 (47) 6 (100)	9 (16) 5 (36) 1 (5) 3 (27)	12 (21) 1 (25) 7 (35) 3 (27) 1 (100)	Drowsiness 2 (4), excitability 1 (2), numbness and tingling 2 (4), nocturnal enuresis 1 (2)

Table 31.2 *Continued*

Reference	No. of evaluated pts	Age range	Diagnosis/seizure type	Therapeutic regimen	Follow-up period	Seizure decrease – number (%) of pts			Adverse effects – number (%) of pts
						90–100%	>50%	n/s	
Ross [28]	63	17 children 46 adults	11 petit mal only 30 petit mal and grand mal 12 temporal lobe 10 miscellaneous	125–750 mg/day add-on	2–6 m	1 (9) 1 (3)		10 (90) 29 (97) 12 (100) 10 (100)	Nausea, dizziness, tingling in 5 (8)
						Follow-up			
						3 m 3 y			
Lombroso and Forsythe [29]	277	201 < 12 y 47 12–19 y 29 > 20 y	91 petit mal 19 grand mal 61 grand mal and petit mal 24 psychomotor 82 mixed	8–30 mg/kg 250–1500 mg >50% mono	3 y	38 (42) 9 (10) 12 (63) 1 (5) 6 (26) 0 (0) 25 (30) 0 (0)			Drowsiness, anorexia, irritability, nausea, vomiting, enuresis, paraesthesiae, headache, dizziness, hyperventilation in 30 (11)
Chao and Plumb [30]	178	3 m to 40 y	All seizures: 55 convulsive equivalent 50 symptomatic 20 temporal 28 other focal 18 generalized idiopathic 7 massive spasm	15–30 mg/kg 20 pts mono 158 pts add-on	3 m–3 y	76 (43) 30 (55) 17 (34) 8 (40) 8 (29) 13 (72)	44 (25) 13 (24) 12 (24) 6 (30) 8 (29) 5 (71)	58 (32) 12 (21) 21 (42) 6 (30) 12 (42) 5 (28) 2 (29)	Anorexia 27 (15), vomiting 10 (6), drowsiness 11 (6), irritability 8 (4), headache 7 (4), fatigue 6 (3), dizziness 5 (3), enuresis 5 (3), paraesthesiae 4 (2); ataxia, depression, irregular respiration, polyuria, poor sleep, skin rash (1)
						At 2-year follow-up			
Forsythe *et al.* [31]	54	3–14 y	40 grand mal 14 temporal lobe seizures	10–15 mg/kg add-on	2–5 y	16 (40) 7 (50)	8 (20) 2 (14)	16 (40) 5 (36)	Drowsiness 3 (5), ataxia 3 (5), nausea and vomiting 1 (2), paraesthesiae 1 (2), school work deterioration 2 (4)
Oles *et al.* [32]	48	6–64 y	Partial seizures	3.8–22 mg/kg add-on	1–30 m	7 (15)	14 (29)	27 (56)	Lethargy 4 (8), paraesthesiae 6 (12), anorexia 2 (4), nausea 3 (6), diarrhoea 2 (4), headache 1 (2), visual changes 1 (2)
Resor and Resor [33]	31		Juvenile myoclonic epilepsy: 31 GTCS 31 myoclonus	500–1750 mg mono	10–70 m	14 (45) 4 (13)		17 (55)	Occasional paraesthesiae, transient diuresis, weight loss 4 (13), renal calculi 6 (30)
Lim *et al.* [34]	20	16–43 y	Catamenial epilepsy: 10 temporal 8 extratemporal 1 generalized 1 not classified	125–750 mg add-on			8 (40)		Dizziness 3 (15), polyuria 3 (15)
Katayama *et al.* [35]	37	1–17 y	All epilepsies: 20 localization related 6 generalized 11 undetermined	10–20 mg/kg add-on	1 m to 10 y	9 (24)	6 (16)	22 (60)	Transient drowsiness in some pts

add-on, add-on treatment; GTCS, generalized tonic–clonic seizures; m, months; mono, monotherapy; n/s, no significant effect; pts, patients; w, weeks; y, years.

Hodge [23] reported on the efficacy of acetazolamide in patients with petit mal only. Oles *et al*. [32] referred to patients with partial epilepsy, and Resor and Resor [33] treated patients with juvenile myoclonic epilepsy. Many studies were relatively short term and followed the patients for several weeks [24,25] or months [22,23,26,28]. Only a few long-term studies have been conducted [18,21,29,30,35].

All the trials of acetazolamide in epilepsy except one [20] have been open label, non-randomized and uncontrolled. The only double-blind placebo-controlled study was performed by Millichap [20] in 14 children with refractory seizures secondary to brain injury. Except for one child who had myoclonic jerks alone, major seizures occurred in all patients. Acetazolamide tablets and placebo were given alternatively to successive patients in a double-blind fashion as an add-on to the existing medications. Initially, 375 mg was given daily and, according to response, the dose was increased at intervals of 2–4 weeks up to a maximum of 750 mg daily. After an adequate trial of the treatment, which varied in duration according to the response, the alternative preparation was substituted. The anticonvulsant effect of acetazolamide was also compared with that of phenytoin in five patients. The follow-up period was 5–26 weeks. Acetazolamide was superior to placebo, and comparable to phenytoin. In 8 of the 14 (57%) patients the maximal seizure reduction was more than 75%, and in five (36%) of the patients a similar control was obtained at the end of the trial period. However, most patients became tolerant to the antiepileptic effect of the drug. Some studies reported more disappointing results. Livingston *et al*. [22] evaluated a series of 58 children with various types of seizures that were treated with acetazolamide. While there was a decrease in the frequency of seizures in a few patients, no patient became seizure free. Ross [28] conducted a study on 63 patients with idiopathic, temporal lobe and symptomatic epilepsy. Only two children with petit mal had a prolonged response over 1 year, and two patients (one with idiopathic epilepsy and one with temporal lobe epilepsy) had a temporary reduction of seizures.

Absence seizures

The rate of control of absence seizures with acetazolamide varies across studies from 0% [22] to 97% [23]. All the studies performed were uncontrolled. Acetazolamide was administered as monotherapy and as an add-on drug.

Lombroso *et al*. [18] investigated 126 patients, comprising 29 patients with petit mal only, 41 with petit mal and other seizures, and 56 with seizures other than petit mal. Patients with petit mal only showed a 90–100% reduction of seizures in more than one-third of the studied cases. Interestingly, the patients who improved the most were those whose electroencephalogram (EEG) showed three spike–waves per second and had prominent slowing in the EEG during hyperventilation. In fact, Saldias *et al*. [61] showed that intravenously administered acetazolamide abolishes or decreases the paroxysmal slow-wave discharges provoked by hyperventilation. Better response to treatment with acetazolamide in patients with three spike–waves per second and with prominent slowing in the EEG pattern during hyperventilation was also reported by Chao and Plumb [30] but not by others [21,25,27].

Ansell and Clarke [21] evaluated 26 patients. Of the five patients in this group who had petit mal seizures, three showed an excellent response. In a long-term follow-up study, Lombroso and Forsythe [29] described 91 (33%) patients who had petit mal seizures, 48 (53%) of whom were treated with acetazolamide alone. A 90–100% improvement in seizure control was observed in 42% of patients for 3 months, in 25% for 1 year and in only 10% for 3 years. In 43 patients who had 50% control of their seizures, acetazolamide was used adjunctively. Following the addition, 44% had a 90–100% seizure reduction for 3 months, but this declined to 7% by 3 years. Golla and Hodge [23] treated 78 patients of different ages with petit mal seizures only by adding 250 mg acetazolamide to their previous therapy. Only two (3%) failed to improve, 34 (44%) became seizure free and the others (53%) improved significantly. The partial tolerance that the majority of patients developed after 3 months was responsive to an increase in dosage to 500 mg daily. Holowach and Thurston [27] used acetazolamide in 56 children with different types of seizures. Of 14 patients with petit mal, nine had complete remission of seizures and in five partial control was achieved. In contrast, Livingston *et al*. [22] found no improvement in 15 patients with absence seizures following treatment with acetazolamide, and in the study conducted by Ross [28], only 1 out of 11 patients with petit mal became seizure free on acetazolamide.

Myoclonic seizures

Lombroso and Forsythe [29] described 15 children aged from 6 months to 7 years with massive myoclonus who were treated with acetazolamide monotherapy: 20% had 90–100% seizure control after 3 months. However, long-term treatment probably resulted in tolerance because no patient maintained this degree of control by the second and third years of follow-up. Chao and Plumb [30] reported fair improvement in five out of seven patients with massive spasms; by contrast, Baird and Borofsky [26] noted no improvement in 16 children with infantile myoclonic seizures who received acetazolamide daily as monotherapy. In a case report of acetazolamide as an add-on drug, a dramatic improvement of action myoclonus was recorded in two patients with progressive myoclonic epilepsy [62].

Acetazolamide monotherapy (dosage range 500–1750 mg daily) was evaluated in patients with juvenile myoclonic epilepsy in a retrospective study by Resor and Resor [33]. Although initially all the patients reported complete control of myoclonus, on a long-term basis only a few remained free of myoclonic jerks.

Generalized tonic–clonic seizures

Many studies that describe patients with generalized tonic–clonic seizures do not differentiate between primary and secondary generalized seizures. Ansell and Clarke [21] described 26 patients, six of whom had 'major idiopathic epilepsy' and were treated with acetazolamide as monotherapy. Marked improvement was noted at the beginning in all patients, but only three patients remained seizure free over a follow-up of 18 months.

In the study by Resor and Resor [33], 51 patients with juvenile myoclonic epilepsy were treated with acetazolamide either because of poor response to conventional antiepileptic drugs or to avoid valproate-associated adverse effects. Fourteen out of 31 patients (45%) who had generalized tonic–clonic seizures became seizure free for 10–70 months. Holowach and Thurston [27] administered acetazolamide to four patients with grand mal seizures who

had not been controlled on their previous medications, and in three of them complete remission was noted. Of the 277 patients studied by Lombroso and Forsythe [29], 19 had grand mal seizures only. In 15 patients, acetazolamide was given as add-on treatment, and as monotherapy to the remaining four. A 90–100% improvement in seizure control was observed in 63% of all patients after 3 months, in 37% after 1 year, in 11% after 2 years and only in 5% at the end of 3 years.

In another study, Forsythe *et al*. [31] evaluated acetazolamide as an add-on treatment to carbamazepine in 54 children, 40 of whom had exclusively grand mal seizures. Twenty-four (60%) patients with generalized seizures had a seizure frequency reduction of 50–100% at the 2-year follow-up. Relapse or no control after 2 years was noted in 16 children. In contrast to the above studies, Ross [28] and Livingstone *et al*. [22] found no improvement in patients with major motor seizures following treatment with acetazolamide.

Focal seizures

Lombroso and Forsythe [29] conducted a long-term follow-up study of 24 patients with psychomotor seizures; six (26%) became seizure free after 3 months, but only 10% had a 90–100% seizure reduction for 1 and 2 years, and after 2 years none was seizure free. Chao and Plumb [30] evaluated retrospectively the value of acetazolamide in 178 patients of different ages, 48 of whom had temporal lobe or other focal seizures. In 16 (33%) of these patients, an 80–100% improvement was reported, and 14 (29%) had more than a 50% seizure reduction. Holowach and Thurston [27] used acetazolamide in 20 children with focal epilepsy who had not been controlled on their previous medications. In 12 (60%) of these children, over 90% seizure reduction was reported.

Forsythe *et al*. [31] evaluated the long-term effect of acetazolamide as add-on treatment to carbamazepine in 54 children, 14 of whom had temporal lobe seizures only. Of these patients, nine (64%) had a reduction in seizure frequency of 70–100% at the 2-year follow-up; however, at the 3- to 5-year follow-up, six of the responders were found to have relapsed.

Oles *et al*. [32] identified retrospectively 48 children and adults with refractory partial seizures who received acetazolamide as adjunct to carbamazepine: 21 (44%) had a greater than 50% decrease in seizure frequency but only three became seizure free, and three lost their response. In a prospective long-term add-on study, Katayama *et al*. [35] investigated 37 patients with refractory epilepsy. Twenty patients had localization-related epilepsy and four of these were reported to be seizure free for more than 3 years. Discouraging results were reported by Ross [28] in 12 patients with temporal lobe epilepsy. In this group, only one had a temporary reduction of seizures and in the other 11 patients there was no apparent effect.

Catamenial seizures

Body water content changes in the premenstrual phase. Gamble suggested that fluid retention has a role in the generation of seizures [63] and that excessive water ingestion facilitates seizures whereas dehydration may have the opposite effect. Acetazolamide has a diuretic action which was thought to contribute to its antiepileptic effects, and this provided the rationale for using this drug in women with catamenial seizures. However, as pointed out by Ansell and Clarke [64], no significant differences in total body water have been observed between women with epilepsy and healthy controls or women with or without catamenial epilepsy treated with acetazolamide.

Although this mechanism of action has been questioned [64], exacerbation of seizures during menstruation was found to respond well and without side-effects to acetazolamide given at dosages of 250–500 mg daily for 5–7 days prior to the onset of the menstrual period and for its duration [65]. In three women with catamenial exacerbation of generalized tonic–clonic or absence seizures, Ansell and Clarke [21] reported that only increasingly higher doses of the drug could maintain seizure control. These authors also described improvement for 3 months in two patients who were given acetazolamide just on the day before and the day of onset of menstruation; a prolonged follow-up, however, was not conducted in these women. Goetting [66] reported a case of post-anoxic myoclonus severely exacerbated premenstrually: 1000 mg acetazolamide given intermittently during 5 days starting at the onset of each exacerbation resulted in prompt and marked improvement. Ross [28], however, observed no response to acetazolamide in 8 of the 25 menstruating females with epilepsy who reported having seizures related to menstruation.

In a retrospective study, Lim *et al*. [34] conducted a telephone questionnaire addressing the relationship of seizures with the menstrual cycle. Twenty women were identified, and acetazolamide was given as an add-on therapy in all patients but one. The drug was given continuously in 55% of women, and intermittently in 45%. A greater than 59% decrease in seizure frequency was reported by 40% of the subjects, and the degree of improvement was similar in both focal and generalized seizures. There was no difference in improvement rates between continuous and intermittent dosing. Loss of efficacy was reported by 15% of patients over 6–24 months.

Tolerance

The use of acetazolamide has been limited by the development of tolerance of patients, and loss of its antiepileptic effects over time has proved to be a major drawback for the use of acetazolamide in epilepsy. Tolerance after prolonged administration of acetazolamide can be demonstrated in animal models, such as the maximal electroshock model [45,48,67,68], and is believed to be mediated by an increased amount and increased activity of carbonic anhydrase in glial cells, as well as proliferation of glial cells [45,67,68]. Patients with epilepsy have been reported to develop tolerance after variable periods of time [18,20,21,29]. Loss of efficacy was noted in some studies after several weeks [20,21] and in other studies after months [18,23] or even years [29,31,35]. The development of tolerance appears to be similar in patients with focal as well as generalized seizures. Once tolerance has developed, withdrawal of the drug for a period of time may occasionally restore the antiepileptic effect [23].

Adverse effects

Acetazolamide is a relatively safe drug. Most of the reported side-effects seem to be related to inhibition of carbonic anhydrase, with the exception of idiosyncratic reactions (Table 31.3).

Table 31.3 Adverse effects of acetazolamide.

Potentially life-threatening effects
Blood disorders: aplastic anaemia, agranulocytosis, thrombocytopenia
Renal failure
Severe skin reactions
Other adverse effects
Gastrointestinal symptoms: abdominal discomfort, nausea, anorexia, diarrhoea
Dysgeusia
Paraesthesia of hands, feet and circumoral region
Increased diuresis
Drowsiness, dizziness, fatigue
Headache
Hyperpnoea, shortness of breath
Metabolic acidosis
Nephrolithiasis
Angle closure glaucoma

Idiosyncratic reactions

Acetazolamide, like other sulphonamide drugs, may induce angle closure glaucoma through a mechanism which is considered to involve an idiosyncratic reaction in the uveal tissues, associated with expansion of the extracellular tissue of the ciliary body and choroid [69]. Immediate cessation of the offending medication is required in such cases.

Isolated cases of acetazolamide-associated aplastic anaemia have been reported. A 73-year-old man treated with acetazolamide 250 mg daily because of oedema of the lower legs developed severe bone marrow depression which resulted in death after 1 month of therapy [70]. Keisu *et al*. [71] reported 11 cases of acetazolamide-associated aplastic anaemia from spontaneous reporting in Sweden over 17 years. Most of the patients were elderly and none was being treated for epilepsy. As most of these patients were being treated with other drugs as well, Shapiro and Fraunfelder [72] questioned whether this relatively high incidence could be attributed to acetazolamide.

Idiosyncratic reactions to acetazolamide also include agranulocytosis, which was described in a 66-year-old woman treated with 250 mg of acetazolamide as an adjunct to digitalis and a low-salt diet because of atherosclerotic heart disease and peripheral oedema [73]. An 85-year-old man treated for congestive heart failure with acetazolamide, 750 mg daily, developed acute thrombocytopenia [74]. Acute renal failure has been described on rare occasions [75]. There are also a number of acute skin reactions attributed to acetazolamide, some of which can be severe, and similar to other sulphonamide derivatives, cases of Stevens–Johnson syndrome have been reported. Cross-sensitivity to acetazolamide in patients allergic to sulpha drugs can occur [76].

Common non-idiosyncratic adverse effects

These adverse effects are encountered mainly upon initiation of therapy and are mostly transient. Patients with glaucoma, perhaps because of their age, are less tolerant to the drug [77], whereas patients with epilepsy tend to have fewer adverse effects [29]. The most common side-effects include drowsiness, fatigue, dizziness, paraesthesia of hands and feet, gastrointestinal symptoms such as nausea, vomiting and diarrhoea, loss of libido, diuresis, headache and hyperventilation (Tables 31.2 and 31.3) [8,18–21,24,25,27–34,78]. In the largest study of 277 patients by Lombroso and Forsythe [29], 11% of patients reported the following adverse effects, in descending order of frequency: drowsiness, anorexia, irritability, nausea, vomiting, enuresis, headache, thirst, dizziness and hyperventilation. These effects have been reported in 8–30% of epilepsy patients in most studies [18–21,24,25,27–34]. Transient distortion of normal taste secondary to acetazolamide was ascribed to carbonated and non-carbonated beverages and food, and was speculated to be due to altered taste receptors secondary to inhibition of carbonic anhydrase [79].

Favourable side-effects have been occasionally noted during treatment with acetazolamide, including improved behaviour and mental status [18,25].

Other adverse effects

Metabolic acidosis

Acetazolamide may induce metabolic acidosis by inhibiting carbonic anhydrase in the proximal tubular epithelium of the kidney, which leads to diuresis, excessive excretion of sodium and potassium ions, and alkaline urine. Although the metabolic acidosis that is produced is mild, it can sometimes be symptomatic, especially in elderly patients and in patients with renal failure [80].

In a study by Epstein and Grant [77], 44 out of 92 (48%) patients treated with acetazolamide for chronic glaucoma complained of a symptom complex syndrome that included malaise, fatigue, weight loss, depression, anorexia and often loss of libido. Patients with this syndrome were found to be significantly more acidotic. Although these symptoms are frequently associated with mild metabolic acidosis and perhaps with a subclinical respiratory acidosis, the central nervous system nature of these adverse effects suggests that inhibition of brain carbonic anhydrase may also have been important in their pathogenesis. Symptoms of metabolic acidosis develop slowly and are often difficult to diagnose, especially in the elderly. The best-documented treatment is supplementation with sodium bicarbonate 56–70 mmol daily orally [77]. Sodium acetate administration has also been reported to be helpful [81].

Metabolic acidosis associated with acetazolamide has been speculatively linked to growth suppression in children receiving acetazolamide in combination with other antiepileptic drugs [82].

Renal stones

Acetazolamide may facilitate the formation of renal stones by inducing partial renal tubular acidosis, with resulting hypercalciuria and hypocitraturia, both of which are recognized risk factors for stone formation [83]. The occurrence of nephrolithiasis with acetazolamide has been of special concern in patients treated for epilepsy [33] and glaucoma [84]. The frequency of stone formation varies across studies. It was very rare in children with epilepsy (i.e. 1 in 277) [29] and was absent altogether in 28 patients examined for renal calculi formation in Katayama's [35] study. However, 6 out of 14 (43%) young adults with juvenile myoclonic epilepsy [33] were reported to have developed renal calculi, without a clear relationship with the administered dosage. Kass *et al*. [84] reported a frequency as high as 12% in patients with

glaucoma. Citrate supplementation and hydration may be effective in reducing stone formation [83].

Effects on bone metabolism

Available data on the effects of acetazolamide on bone metabolism are somewhat contradictory and the role of carbonic anhydrase in human bone resorption is unclear. Acetazolamide may accelerate osteomalacia by different mechanisms, which include urinary calcium and phosphate excretion and systemic acidosis [85]. Mallette [85] described two acetazolamide-treated patients with osteomalacia, but both patients were also receiving barbiturates. In post-menopausal women with glaucoma, long-term (more than 4 years) use of carbonic anhydrase inhibitor therapy was associated with a bone-sparing effect, as judged by spinal bone mineral density [86]. This effect was absent in acetazolamide-treated premenopausal women and in those who received acetazolamide for less than 2 years.

Effects on a fetus and newborn

Layton and Hallesy [87] reported that 36% of the offspring of rats fed with acetazolamide in their diet during pregnancy had a defect confined mainly to the right forepaw. The plasma levels achieved with that diet were of the same order of magnitude as those recorded in patients who receive 500–1500 mg of acetazolamide. A similar effect was observed in mice and hamsters but not in monkeys [88]. A human case of multiple congenital malformations (glaucoma, microphthalmia and patent ductus arteriosus) has been described in a letter from Lederle Laboratories in 1975, cited by Worsham *et al*. [89]. In a neonate of a 22-year-old woman treated with acetazolamide 750 mg daily because of glaucoma, a sacrococcygeal teratoma was described [89].

There are no adequate studies in pregnant women, and therefore the teratogenic risk of acetazolamide in humans has not been established.

There has been one report suggesting a possible association between treatment for glaucoma throughout pregnancy with 500 mg of acetazolamide and metabolic acidosis, hypocalcaemia and hypomagnesaemia in a single preterm infant [90].

Soderam *et al*. [91] reported that the dose of acetazolamide transferred to the child through breast milk was low, i.e. less than 0.7% of the dose per kilogram of body weight of the mother. Based on their findings, they speculated that breastfeeding by an acetazolamide-treated mother is unlikely to cause harmful effects in the infant.

Place in current therapy

Usefulness and limitations

Evidence on the efficacy of acetazolamide in epilepsy is restricted mainly to retrospective, uncontrolled studies. In these studies, conducted mostly in the 1950s, selection of patients, seizure type, methods and duration of treatment, and definition of response varied extensively, which makes it difficult to evaluate the value of the drug in seizure types and syndromes as currently classified.

Most patients treated with acetazolamide had seizures unresponsive to other antiepileptic drugs. Many studies define acetazolamide as an antiepileptic drug with a broad spectrum of action. Although some authors [22,28] failed to demonstrate its usefulness, efficacy in different types of seizures has been reported in most of the published studies. The best responses were reported in absence seizures [18,23,29], but good results were also described in patients with generalized tonic–clonic seizures [21,29,31,33], myoclonic seizures [29,30,33] and partial seizures [29–32,35]. These data suggest that acetazolamide can be beneficial in a variety of seizure types, and in some of the studies the patients had an initially spectacular effect. Acetazolamide can be helpful mainly as an add-on treatment in children and adults, with special reference to those with generalized seizures, particularly absences, but also in patients with partial seizures. The lack of effect on the hepatic drug-metabolizing enzymes makes acetazolamide valuable when drug interactions are a concern. The antiepileptic effect of acetazolamide develops promptly [27], and therefore the drug may be useful when a rapid onset of effect is needed.

The use of acetazolamide has been limited by the frequent development of tolerance. Loss of seizure control has been reported as early as several weeks after instituting treatment or after months and years, and occasionally an increase in dosage has been required to maintain a sustained effect. As cyclical dosing may reduce the development of tolerance, acetazolamide has been proposed as adjunct intermittent therapy in the management of catamenial epilepsy. However, controlled studies in women with catamenial seizures are required before acetazolamide can be recommended for this indication in routine clinical use. Other antiepileptic drugs, particularly benzodiazepines, are also known to be subject to the development of tolerance. A comparison between the degree of tolerance associated with acetazolamide and benzodiazepines has not been performed.

In this author's opinion, acetazolamide has been too quickly abandoned in favour of newer antiepileptic drugs without having undergone adequate evaluation for its potential value. In some patients, a dramatic effect has been observed, and a worthwhile effect has been reported in different types of epilepsy. Its major drawbacks are the potential for tolerance and the risk of idiosyncratic reactions. The former, however, does not occur in all patients and the latter is rare. Acetazolamide is simple and easy to use and is generally well tolerated. Even though its usefulness is likely to be limited, acetazolamide warrants re-evaluation by modern methodological standards.

Dosing recommendations

Dosages used in different studies in children and adults with epilepsy have varied from 3 to 36 mg/kg/day, whereas total dosages varied from 125 mg to 1750 mg.

The recommended maintenance dose for adults is 10–20 mg/kg, or 500–1000 mg/day, given 2–3 times daily [50,60]. Plasma levels with this dosage were reported to be 10–14 μg/mL [50]. The doses reported for children were 10–36 mg/kg [20,29,31]. Lombroso and Forsythe [29] noted that in adults and children increasing dosage above 750 mg was rarely effective and that 500 mg/day was usually the maximal useful dose in children less than 7 years of age. Monitoring plasma concentration has not been found to be generally helpful [32].

Table 31.4 High-risk groups.

Elderly patients
Patients with concomitant disorders
Renal failure
Hepatic failure
Adrenal insufficiency
Conditions associated with sodium and potassium depletion
Sulfonamide hypersensitivity
Acidotic disorders
Patients on specific co-medications or diets
Drugs causing sodium and potassium depletion
Drugs causing lithiasis or metabolic acidosis (e.g. topiramate)
Diets causing metabolic acidosis (ketogenic diet)

The starting dose should be 125 mg twice daily in children and 250 mg twice daily in adults, and it may be increased at weekly intervals. Before making the decision to increase the dosage, it should be considered whether tolerance has occurred to adverse effects and seizure control. Slow discontinuation over several weeks is recommended to prevent withdrawal seizures [60].

Individuals at higher risk include older patients with compromised renal function, who should be started out with a reduced dose to avoid acidosis [92].

Precautions and contraindications

Experience with acetazolamide shows that it is a relatively safe agent, and that it can be used for long periods without serious adverse effects. Because of rare cases of aplastic anaemia, agranulocytosis and thrombocytopenia (Table 31.3), a full blood count before initiating treatment is recommended. The usefulness of repeated haematology tests is unknown.

Patients with impaired renal function require a lower dosage, because the clearance of acetazolamide correlates with creatinine clearance [56]. Liver disease is a contraindication to the use of acetazolamide. Alkalinization of urine diverts ammonia of renal origin from urine to the systemic circulation, potentially causing hepatic encephalopathy [93]. Because of its tendency to cause potassium loss, acetazolamide is also contraindicated in Addison's disease and in adrenal insufficiency.

When acetazolamide is given with carbamazepine, monitoring of serum sodium may be indicated because both drugs may cause hyponatraemia [50], and carbamazepine levels should also be measured [31]. Special attention to ensure appropriate hydration and to monitor for potential metabolic acidosis is required if acetazolamide is given in combination with topiramate or zonisamide, because all three drugs inhibit carbonic anhydrase and may cause lithiasis and acidosis (Table 31.4).

Acetazolamide is an animal teratogen [87,88], and two cases of possible human teratogenicity related to acetazolamide have been described [89]. This should be taken into consideration when treating women of childbearing age.

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32 Adrenocorticotropic Hormone and Corticosteroids

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	Adrenocorticotropic hormone (ACTH)	Prednisone/prednisolone
Primary indication	First-line treatment for infantile spasms. May be of value in other paediatric epileptic encephalopathies	First-line treatment for infantile spasms. May be of value in other paediatric epileptic encephalopathies
Usual preparations	HP Acthar® Gel: 5 mL vial (80 USP units/mL) for intramuscular or subcutaneous use Synachten Depot®: 0.5 mg/1 mL, 0.5 mg/0.5 mL, 1 mg/1 mL, 2 mg/2 mL, for intramuscular use	Prednisone: tablets: 1, 2.5, 5, 10, 20, 50 mg; oral solution: 1 mg/mL Prednisolone: tablets: 5 mg; oral solution: 3 mg/mL
Usual dosage	2 IU/kg/day intramuscularly or subcutaneously (indicative dosage – dosing schedules vary markedly across centres and countries). After an appropriate period, dosage is down-escalated gradually	2 mg/kg/day orally. After an appropriate period, dosage is down-escalated gradually
Significant drug interactions	Barbiturates may decrease the effect of ACTH	Enzyme-inducing drugs increase the metabolic clearance of prednisolone. Many drugs can inhibit the metabolism of prednisolone
Serum level monitoring	Not useful	Not routinely performed
Target range	Not applicable	Not applicable
Common/important adverse effects	Irritability, hypertension, gastritis, peptic ulcer, headache, increased intracranial pressure, increased intraocular pressure, infections, immunosuppression, suppression of the hypothalamic–pituitary–adrenal axis, Cushing's syndrome and other endocrine disorders, electrolyte disturbances, transient cerebral atrophy, myocardial hypertrophy, pancreatitis, myopathy, cataracts, osteoporosis, aseptic necrosis of femoral or humeral heads, reduced growth rate, hypersensitivity reactions	Irritability, hypertension, gastritis, peptic ulcer, headache, increased intracranial pressure, increased intraocular pressure, infections, immunosuppression, suppression of the hypothalamic–pituitary–adrenal axis, Cushing's syndrome and other endocrine disorders, electrolyte disturbances, transient cerebral atrophy, myocardial hypertrophy, pancreatitis, myopathy, cataracts, osteoporosis, aseptic necrosis of femoral or humeral heads, reduced growth rate

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	Adrenocorticotropic hormone (ACTH)	Prednisone/prednisolone
Main advantages	High response rates in infantile spasms and extensive clinical experience	Good response rates, oral route of administration, feasibility of longer-term treatment
Main disadvantages	Parenteral route of administration, higher risk of serious adverse effects compared with corticosteroids, optimal dose and duration of treatment not established	Possibly less efficacious than ACTH in controlling infantile spasms. Significant adverse effects, particularly with prolonged treatment
Mechanism of action	Antiepileptic actions might be related to anti-inflammatory and immunosuppressant properties, as well as to inhibition of corticotropin-releasing hormone release	Antiepileptic actions might be related to anti-inflammatory and immunosuppressant properties, as well as to inhibition of corticotropin-releasing hormone release
Oral bioavailability	Not applicable	Prednisone: over 70% (in terms of metabolically derived prednisolone)
Time to peak levels after single dose	Within 1–2 h. May be delayed with sustained-release formulations	Within 1–2 h
Main routes of elimination	Enzymatic hydrolysis	Oxidative metabolism and conjugation
Volume of distribution	0.4 L/kg (value refers to 1–24β-tetracosactide, the principle contained in Synachten Depot)	0.5–0.9 L/kg (prednisolone). Volume of distribution increases with increasing doses
Elimination half-life	About 15 min, but plasma levels remain sustained for many hours when using sustained-release formulations	1.3–4 h (prednisolone), with shortest values in children and in patients taking enzyme inducers
Plasma clearance	–	1.5–6.5 mL/min/kg (prednisolone), with highest values in children, in patients taking enzyme inducers and in patients on high doses
Protein binding	–	55–95% (prednisolone). Binding decreases with increasing drug concentration
Active metabolites	Activity resides primarily in the first 20 amino acids from the N-terminal end of the chain. Partial loss of activity is observed with progressive shortening of the chain beyond the 20 amino acid residues	The effects of prednisone are mediated practically entirely through conversion to prednisolone
Comment	Considered by many authors the agent of choice for the treatment of infantile spasms, particularly in patients who do not have tuberous sclerosis	A valuable alternative to ACTH in the treatment of infantile spasms. May be valuable for longer-term treatment of other paediatric epileptic encephalopathies

Introduction

In 1958, Sorel and Dusaucy-Bauloye [1] discovered almost serendipiditously that adrenocorticotropic hormone (ACTH or corticotropin) was efficacious in controlling seizures and improving electroencephalogram (EEG) abnormalities as well as neuropsychological performance in patients with infantile spasms. The importance of this finding is noteworthy, since infantile spasms represent a severe epileptic condition which is associated with encephalopathic symptoms and an unfavourable cognitive outcome. Since then, several other publications have confirmed the efficacy of ACTH and corticosteroids in the treatment of spasms. These agents have also been applied – and continue to be applied – to the treatment of other severe forms of childhood epilepsy, even though there is a paucity of high-quality studies demonstrating their efficacy in these conditions [2].

ACTH and corticosteroids are mostly used to treat epileptic encephalopathies, a group of severe clinical entities with heterogeneous clinical presentations and variable causes. The latter include prenatal causes such as brain malformations, chromosomal abnormalities and neurocutaneous disorders, perinatal causes such as hypoxic–ischaemic injuries and neonatal hypoglycaemia, and postnatal causes such as vascular or infectious insults. Brain lesions associated with these conditions may be diffuse or focal, either uni- or bilateral. 'Idiopathic' cases are exceptional.

In epileptic encephalopathies, interictal epileptiform EEG abnormalities play a significant role in generating progressive disturbances of cerebral function. Thus, the aim of treatment is not limited to seizure control, and more often the greatest challenge is to improve the child's psychomotor development, a goal which requires suppression or reduction of interictal EEG discharges.

Chemistry

Corticotropin is a 39-amino-acid polypeptide secreted from the anterior pituitary (Fig. 32.1). Its biological activity resides in the first 20 amino acids from the N-terminal end of the chain. Human, sheep, cattle and swine corticotropin have different structures, but the first 20 amino acids are the same and, therefore, they are considered to exert identical biological effects. Commercial sources of natural ACTH generally are obtained from porcine pituitaries. Among the formulations most commonly used in epilepsy therapy, HP Acthar® Gel contains natural ACTH, while Synachten Depot® and Cortrosyn-Z® contain a polypeptide made up of the first 24 amino acids of natural ACTH.

The corticosteroids most commonly used in epilepsy therapy are prednisone, prednisolone and hydrocortisone. Prednisone [molecular formula $C_{21}H_{26}O_5$, molecular weight 358.44 (Fig. 32.1)] is a white crystalline powder very slightly soluble in water and slightly soluble in alcohol and chloroform. Prednisolone [molecular formula $C_{21}H_{28}O_5$, molecular weight 360.45 (Fig. 32.1)] is a white crystalline powder, very slightly soluble in water. Hydrocortisone (molecular formula $C_{21}H_{30}O_5$, molecular weight 362.46) is also a white crystalline powder, very slightly soluble in water and sparingly soluble in acetone and alcohol.

Mechanisms of action

Little is known on the mechanisms of the antiepileptic action of ACTH and corticosteroids, partly because little is known about the pathogenesis of epileptic encephalopathies. Various hypotheses, however, have been put forward.

In vitro, ACTH and corticosteroids stimulate the growth of neuroblasts [3], a property that might be of particular relevance for the treatment of encephalopathies occurring in the first year of life. ACTH and corticosteroids may also modulate various neurotransmitter systems. In particular, ACTH down-regulates serotonin 5-HT_2 receptors in the cerebral cortex, and modulates γ-aminobutyric acid (GABA) and dopamine receptors, an effect which, in animal models, is age dependent [4].

In addition, ACTH and corticosteroids have well-established immunosuppressant properties. In the last few years, increasing evidence has accumulated that certain forms of severe epilepsy have an inflammatory and/or immunological basis [5]. Hence, the antiepileptic actions of ACTH and corticosteroids, as well as immunoglobulins, may depend on their anti-inflammatory and immunosuppressant effects.

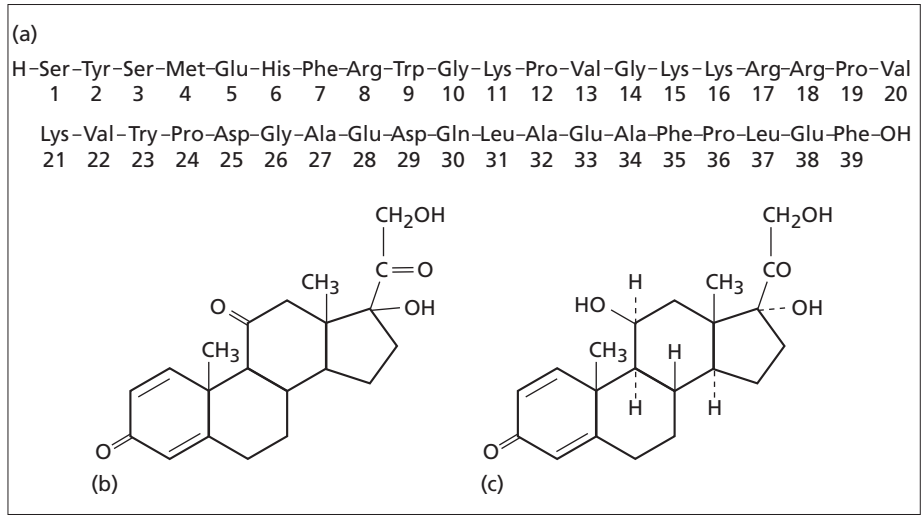

Fig. 32.1 Chemical structure of (a) ACTH, (b) prednisone and (c) prednisolone.

ACTH probably acts not only by releasing endogenous corticosteroids but also by a direct action on the central nervous system (CNS). In fact, even though ACTH fragments that do not induce the endogenous release of corticosteroids are ineffective against infantile spasms, ACTH has been found to retain efficacy against spasms in patients with adrenal insufficiency [6] or in the presence of adrenal inhibition [7]. ACTH increases the synthesis of RNA and DNA and promotes brain maturation and growth through mechanisms such as stimulation of myelinization and dendritic sprouting [8–10]. The penetration of ACTH across the blood–brain barrier in humans is unknown, but it is estimated to be quite low [10,11]. However, recently, a direct action of ACTH on amygdala neurones via activation of central melanocortin receptors has been postulated, supporting the notion that a direct, steroid-independent action may account for some of the effects of ACTH in the CNS. The binding of ACTH to melanocortin receptors on limbic neurones leads to a significant down-regulation of corticotropin-releasing hormone (CRH) gene expression, which may provide a mechanism for the efficacy of ACTH in some human epilepsies (see below) [12]. The affinity of different analogues, fragments and formulations of ACTH for these central receptors is very different from their affinity for peripheral receptors involved in steroid release. This might explain the variability in ACTH therapeutic efficacy reported in different studies in infantile spasms, in which different ACTH preparations have been used. For example, it is possible that synthetic preparations are more potent in activating melanocortin receptors than natural preparations.

At present, the most accredited hypothesis is that ACTH and corticosteroids exert their actions through the hypothalamic–pituitary–adrenal axis [12]. This hypothesis stems primarily from studies related to infantile spasms. In 1985, Nalin *et al.* [13] described decreased ACTH levels in the cerebrospinal fluid (CSF) of children with infantile spasms. It is plausible that decreased ACTH levels are associated with higher CRH levels, and it has been postulated that conditions causing infantile spasms activate a 'stress response', leading to increased CRH production and release [12]. CRH has a proconvulsant action by increasing neuronal excitability in the limbic system and the brainstem, and low concentrations of endogenous ACTH and corticosteroids increase CRH levels in the CNS [12,13]. Hence, exogenous ACTH and corticosteroids might act through a negative feedback mechanism by suppressing CRH synthesis and release. According to Jaseja [14], this hypothetical mechanism may also explain the putative superiority of ACTH over oral corticosteroids in the management of infantile spasms. Indeed, ACTH has a double action in inhibiting CRH secretion, one which involves a direct effect and one which is mediated by increased blood levels of endogenous corticosteroids. By contrast, corticosteroids exert a direct inhibiting action on CRH secretion, but their inhibiting action on endogenous ACTH secretion may indirectly attenuate their influence on CRF release.

In 1992, Mares and Velisek [15] developed an animal model of tonic seizures, considered equivalent to infantile spasms, in which seizures were induced in rats by intraperitoneal injection of *N*-methyl-D-aspartate (NMDA) on postnatal day 15. In 2007, the same group reported an refinement of this model by combining prenatal exposure to betamethasone with postnatal administration of NMDA, and demonstrated that prenatal exposure to the steroid sensitizes the rats to development of NMDA-induced spasms [16]. Interestingly, rats exposed prenatally to betamethasone were much more responsive to ACTH treatment, compared with animals unexposed to betamethasone. Imaging studies in these rats have shown that limbic areas, the hypothalamus and the brainstem are primarily involved in the generation of NMDA-induced spasms [16]. These areas correspond to those targeted by CRH. These data seem to support the hypothesis that prenatal stress facilitates the onset of spasms and that ACTH may act by antagonizing the stress response. This pathogenetic hypothesis may apply in particular to some cases of infantile spasms, such as those secondary to perinatal hypoxic–ischaemic injury, whereas it is more difficult to envisage a role for this mechanism in 'idiopathic' or 'cryptogenic' cases with no evidence of pre- or perinatal stress.

The animal model developed by Velisek and colleagues [15,16] shows seizures phenotypically similar to human infantile spasms, associated with similar ictal EEG discharges. However, these animals do not display the abnormal interictal EEG pattern called hypsarrhythmia, and the condition does not persist beyond the acute injection period. On the other hand, the tetrodotoxin animal model [17] resembles more closely the human condition. In this model, tetrodotoxin is chronically infused into the developing hippocampus neocortex of infant rats on postnatal days 10 to 12. After a minimum latency of 10 days, one-third of tetrodotoxin-exposed rats develop spasms in clusters and interictal multifocal EEG spikes and sharp waves. No data are available so far on the effect of ACTH or corticosteroids in this model.

Pharmacokinetics

ACTH

Since ACTH is rapidly degraded by proteolytic enzymes in the gastrointestinal tract, it must be administered parenterally by intramuscular or by subcutaneous route [18]. The formulations used in epilepsy treatment are not suitable for intravenous use. Natural ACTH is readily absorbed from the injection site, but with sustained-release preparations absorption is prolonged for several hours. In the USA, a natural preparation of ACTH is generally used [19], whereas synthetic preparations are commonly used in Europe and Japan [20,21]. The US preparation, Acthar Gel®, is a highly purified sterile formulation of ACTH in 16% gelatin, which provides a prolonged release of the hormone [22]. The European formulation, Synachten Depot®, is a long-acting synthetic 24-amino-acid polypeptide and zinc complex that shows the same biological activities as natural ACTH [23]. The most widely used synthetic analogue in Japan, where natural ACTH is not commercially available, is Cortrosyn-Z®, a zinc hydroxide suspension of a 24-amino-acid polypeptide similar to Synachten Depot®. Synachten Depot® and Cortrosyn-Z® exhibit the full range of activities of natural ACTH.

In humans, the plasma half-life of ACTH is about 15 minutes and elimination is due to rapid enzymatic hydrolysis [18]. With the commonly used sustained-release preparations, however, plasma levels are maintained for many hours after the injection in spite of the short elimination half-life.

Corticosteroids

Prednisone and prednisolone are the most commonly prescribed oral corticosteroids. Prednisone itself is virtually inactive and is

rapidly converted in the liver, partly through a first-pass effect, to prednisolone, which is found in plasma at much higher concentrations than prednisone itself and is responsible for the pharmacological effects.

Both prednisone and prednisolone are rapidly absorbed from the gastrointestinal tract. The active moiety, prednisolone, is highly bound (60–95%) to plasma proteins, particularly transcortin, and its fraction unbound increases with increasing drug concentration. Partly because of concentration-dependent protein binding, the clearance of total (bound + unbound) prednisolone increases with increasing dose [24]. Prednisolone clearance is also higher in children than in adults [25] and in patients co-medicated with enzyme inducers [26]. The half-life of prednisolone is in the range of 1.5–4 h, the shortest values being observed in children and in patients co-medicated with enzyme inducers. Elimination of prednisolone is primarily metabolic, with CYP3A4-mediated oxidation playing a major role in addition to other enzymes.

Hydrocortisone is the synthetic form of naturally occurring cortisol. The oral bioavailability of hydrocortisone is estimated to be close to 100% [27] and is not expected to be influenced by gender, age or liver disease [28,29]. Because of its high oral bioavailability, orally administered hydrocortisone is almost equally effective as an identical dose given intravenously. Peak concentrations are reached within 1–2 h, and the plasma half-life is about 1.5 h. Certain water-soluble esters of hydrocortisone and its synthetic congeners may be administered intravenously in order to achieve rapidly high concentrations in body fluids. More prolonged plasma levels can be obtained by intramuscular injection of a suspension of hydrocortisone, its esters and congeners. Under normal circumstances, cortisol is ≥90% bound to plasma proteins, and elimination is predominantly metabolic.

Drug interactions

The metabolism of many corticosteroids, including prednisolone and hydrocortisone, is stimulated by concomitant administration of enzyme-inducing agents such as phenytoin, carbamazepine and barbiturates [26]. This may result in reduced therapeutic efficacy of these steroids. Since ACTH acts partially via corticosteroids, these interactions may also be observed with ACTH.

Inhibitors of CYP3A4, such as certain macrolides, ritonavir and other drugs, reduce the rate of metabolism of corticosteroids and may potentiate their clinical effects.

Serum level monitoring

Although the suggestion has been made that measuring serum levels of corticosteroids may facilitate clinical management by identifying pharmacokinetic variability related to factors such as disease states and drug interactions [25], in practice the measurement of the serum concentration of these agents is not done routinely. Optimization of therapy with ACTH and corticosteroids is best guided by clinical observations, including the monitoring of EEG responses when appropriate.

Efficacy

Infantile spasms

Short-term studies

Since the work of Sorel and Dusaucy-Bauloye [1], ACTH has been used for the treatment of infantile spasms worldwide. Alongside corticosteroids and vigabatrin, ACTH continues to be considered a first-line option for this condition, although there is no consensus on which agent should be used preferentially and, particularly in the case of ACTH, on the optimal dosing schedule.

In assessing the efficacy of ACTH and corticosteroids in infantile spasms, one must remember that the objectives of therapy in this condition are not limited to controlling the seizures but should also include suppression of hypsarrhythmia and improvement of developmental outcome. Assessing these outcomes requires long-term follow-up studies that are very scarce in the literature. With respect to seizure control, the only meaningful outcome in this form of epilepsy is complete disappearance of spasms, since a 50–70% decrease in spasms frequency is clinically irrelevant. Most published studies focus exclusively on short-term results in spasms control. Assessment methodology for this outcome measure is also very important because estimates of seizure control based simply on parents' observations have been shown to differ significantly from those based on prolonged video-electroencephalography monitoring [4].

In 2004, MacKay *et al*. [30] performed an exhaustive meta-analysis of the literature on the medical treatment of infantile spasms. Their worked confirmed that, despite the widespread use of ACTH and steroids, there are few prospective studies and only five randomized trials with these agents. Moreover, treatment protocols differ significantly: for instance, in the studies considered in the meta-analysis, ACTH dosage varied from 0.2 international units (IU)/kg/day up to 150 IU/m^2/day as initial dosage, with duration of treatment at the highest (initial) dose varying from 1 to 6 weeks and a total treatment time ranging from 4 to 12 weeks. Only 14 studies with ACTH met the minimal criteria for inclusion in the meta-analysis. Of these, five were randomized controlled trials (class I–III) [20,31–34], four were prospective open-label trials (class III–IV) [35–38] and five were retrospective case series (class IV) [19,39–42]. Only one study [31] was placebo controlled and only two were cross-over studies of ACTH versus prednisone [31] or vigabatrin [20]. When only short-term effects on seizures were considered, spasm cessation was reported in 42–87% of ACTH-treated patients and occurred within 7–12 days. About one-third of patients showed relapse of spasms within 3 months after completion of the ACTH cycle.

With respect to the relationship between ACTH efficacy and dosage, a 1982 study by Riikonen [43] failed to detect significant differences in terms of spasm control, EEG improvement or incidence of relapses when two groups of patients, one treated with 'high initial doses' (120–160 IU/day) and the other with 'low initial doses' (20–40 IU/day), were compared. However, the 'low doses' used by Riikonen would be considered relatively high by current standards. In fact, in order to reduce adverse effects, increasingly lower doses have been used over time. In 2006, Oguni *et al*. [44] suggested the use of extremely low doses, i.e. 0.2 IU/kg/day, to achieve maximum efficacy with minimal adverse

effects. For the same reasons, the current consensus is also to avoid long treatment schedules and to restrict treatment duration to a maximum of 4–6 weeks.

In the meta-analysis by MacKay *et al.* [30], only five studies with oral corticosteroids met criteria for inclusion. Of these, two were randomized controlled trials (class II and III) [31,33], two were prospective open-label trials (class III) [36,45] and one was a retrospective case series (class IV) [40]. Prednisone or prednisolone was used, at the initial dosage of 2–3 mg/kg/day, for a period ranging from 4 to 20 weeks and then tapered and discontinued. Cessation of spasms was reported in 29–59% of treated cases.

The data on the comparative efficacy of ACTH and oral corticosteroids are controversial, even though some results seem to favour ACTH. In the double-blind trial conducted by Hrachovy *et al.* [31] and comparing ACTH at an initial dose of 20 IU/kg/day with prednisolone at a dose of 2 mg/kg/day in a total of 24 infants with infantile spasms, there was no difference in efficacy between the two treatments. In this study, ACTH and prednisolone were given until a response was obtained, for a maximum of 6 weeks prior to tapering. In contrast, in the single-blind randomized study by Baram *et al.* [33] comparing high-dose ACTH (150 IU/m^2/day) with prednisone 2 mg/kg/day, each given for 2 weeks in a total of 29 infants, 86% of ACTH-treated versus 28% of prednisone-treated infants achieved cessation of spasms and hypsarrhythmia. The treatment of responders was tapered off over 12 days, while non-responders were crossed over to the alternative treatment. The two infants who failed on ACTH received prednisone and responded by both clinical and EEG criteria. Of the 10 infants who failed prednisone, nine received ACTH and eight responded [33]. In another study suggesting a superiority of ACTH over corticosteroids, Snead *et al.* [40] reported cessation of spasms in all of 30 patients with infantile spasms and hypsarrhythmia treated with ACTH and in 59% of 22 patients with infantile spasms and hypsarrhythmia treated with prednisone. ACTH was given at the initial dose of 150 IU/m^2/day for 1 week and then progressively decreased, while prednisone was given at the dose of 3 mg/kg/day for 4 weeks and then gradually tapered [40]. On the other hand, Lombroso [36] did not detect any short-term difference in spasms cessation between high-dose ACTH (110 IU/m^2/day for 3 weeks, then tapered off over 5 weeks) and prednisolone (2 mg/kg/day for 8 weeks, then gradually discontinued over 12–24 weeks) in a total of 108 infants.

There are very few data on the use of parenteral corticosteroids. Yamamoto *et al.* [46] performed a comparative study in 10 patients with symptomatic infantile spasms, of whom five were treated with a single intravenous injection of 0.25 mg/kg dexamethasone palmitate administered seven times over a 3-month period (once a week in the first month, once every 2 weeks in the second month and once a month in the third month, which corresponds to a total dosage of 1.75 mg/kg), and five were treated with ACTH intramuscularly at a dose of 0.025 mg/kg/day for 6 weeks (total dosage of 0.625 mg/kg). Spasms and hypsarrhythmia disappeared in all cases, but after 3 months patients in both groups showed either a relapse of spasms or the appearance of partial seizures.

ACTH and corticosteroids are considered first-line agents in all cases of infantile spasms, with the exception of spasms associated with tuberous sclerosis. In a randomized trial, Chiron *et al.* [47] described the cessation of spasms in only 5 out of 11 infants with tuberous sclerosis treated with oral hydrocortisone, whereas all 11 infants treated with vigabatrin became seizure free. Successful treatment of infantile spasms with vigabatrin has also been reported in infants without tuberous sclerosis. In 2004, Lux *et al.* [48] conducted a randomized trial comparing vigabatrin 100 mg/kg/day with hormonal therapy (ACTH 40 IU on alternate days or prednisolone 40 mg/day) in 107 patients with infantile spasms not associated with tuberous sclerosis. After 2 weeks of treatment, spasms cessation was achieved in 40 of 55 (73%) patients randomized to hormonal treatment, compared with only 28 of 52 (54%) infants randomized to vigabatrin [48], even though long-term seizure outcome did not differ between the two treatments (see below) [49]. Evidence for a superior efficacy of ACTH over vigabatrin in infantile spasms not associated with tuberous sclerosis, at least in the short-term, has also been provided in a randomized study by Vigevano and Cilio [20].

Long-term studies

Long-term effects on spasms and on developmental outcome are difficult to evaluate. Frost and Hrachovy [4] reviewed 44 studies addressing this issue and reported an average persistence of seizures in 53% of patients after a follow-up period of minimum 31 months, with a very large variation across studies (9–86%). Most of the patients had been treated with ACTH or corticosteroids, but also with additional drugs. Cryptogenic cases were associated with a more favourable long-term outcome.

In the case series of 64 cryptogenic and symptomatic infants with infantile spasms described by Glaze *et al.* [50], there were no significant differences in outcome between those treated with ACTH and those treated with prednisone. In a prospective study of 102 cryptogenic cases comparing ACTH with other therapies such as oral steroids, benzodiazepines or conventional antiepileptic drugs (AEDs), Lombroso [36] found a significant difference in favour of ACTH for psychometric development and for achievement of a seizure-free state. In the multicentre randomized trial by Lux *et al.* [48] that found hormonal treatment (ACTH or prednisolone) more efficacious than vigabatrin in the short term, developmental and seizure outcomes were also evaluated at age 14 months. At the final assessment, spasms-free rates were similar in the two groups, with 41 of 55 (75%) patients randomized to hormonal treatment and 39 of 51 (76%) patients randomized to vigabatrin being free from spasms [48]. Neurodevelopmental outcome assessed by using the Vineland Adaptive Behavior Scale (VABS) did not differ significantly between the two groups. However, in cryptogenic patients the mean VABS score was higher in those allocated to hormonal treatment. In interpreting these findings, it should be considered that cryptogenic cases represent a heterogeneous group, since patients initially classified as cryptogenic may be subsequently reclassified as symptomatic as a result of improved diagnostic tools, such as more advanced imaging techniques.

Other epileptic syndromes

Studies on the efficacy of ACTH and corticosteroids in the treatment of other epilepsy syndromes are limited. In a recent Cochrane review, Gayatri *et al.* [2] found only one randomized placebo-controlled trial [51], in which ACTH was administered according

to a double-blind cross-over design in five patients with multiple intractable seizure types and mental retardation or developmental delay. Results were not encouraging in that only three patients had a 25–50% reduction in seizure frequency, and none was seizure free.

Results from some uncontrolled studies have been more favourable. Snead *et al*. [40], in a study of 64 children with intractable seizures including infantile spasms without hypsarrhythmia, myoclonic seizures and different generalized or partial seizures, found that seizure control was achieved in 25 of 34 (73%) children treated with ACTH, but in none of 30 children treated with prednisone. Yamatogi *et al*. [52] treated, with ACTH, 45 patients with Lennox–Gastaut syndrome at doses ranging from 10 to 30 IU/day for a period of 10–57 days. Twenty-three (51%) patients became seizure free for over 10 days, but the majority (78%) later relapsed. In a report by Sinclair [53], 7 out of 10 children with Lennox–Gastaut syndrome who were treated with prednisolone at 1 mg/kg/day for 6 weeks achieved seizure freedom, and three children had a reduction in seizure frequency. EEG, behaviour and communication were also improved, but for how long the improvement was maintained is unclear.

Encouraging results have also been reported in the treatment of patients with Landau–Kleffner syndrome and electrical status epilepticus during slow-wave sleep (ESESS). In particular, Marescaux *et al*. [54] reported cessation of seizures, normalization of the EEG and improved speech with a prolonged 3-month treatment with hydrocortisone or prednisolone in three patients with Landau–Kleffner syndrome. Similar results have been reported in ESESS, but their significance is limited by lack of information on neuropsychological functions and on incidence of relapses during long-term follow-up [55].

Transient improvement in seizure control has been described in patients with Rasmussen's encephalitis treated with corticosteroids [56], but the course of Rasmussen's encephalitis is generally catastrophic and neurosurgery seems to provide the only effective treatment in this condition.

ACTH and corticosteroids do not appear to be efficacious in myoclonic epilepsies, particularly in severe myoclonic epilepsy of infancy (Dravet's syndrome).

Adverse effects

ACTH and corticosteroids may cause significant adverse effects, including hypertension, gastritis and peptic ulcer, irritability, headache, immunosuppression, infections, Cushing's syndrome, electrolyte disturbances (e.g. sodium and fluid retention, potassium and calcium loss, hypokalaemic alkalosis), increased intracranial pressure, increased intraocular pressure, pancreatitis, subcapsular cataracts, aseptic necrosis of femoral and humeral heads, myopathy, transient cerebral atrophy or 'cerebral shrinkage', and suppression of the hypothalamic–pituitary–adrenal axis.

Irritability is present in almost all patients, and 'cerebral shrinkage' is present in about two-thirds of patients [4]. More serious side-effects have been reported, predominantly with ACTH rather than with corticosteroids, and include potentially fatal sepsis, hypersensitivity reactions and myocardial hypertrophy. These complications seem to be more common in patients receiving high-dose ACTH therapy. There is no clear evidence of differences in adverse effects profiles between natural and synthetic ACTH. However, synthetic ACTH is considered to be less antigenic and, therefore, less likely to cause hypersensitivity reactions than the natural preparation.

Prolonged use of corticosteroids, especially when continued for several months, typically leads to immunosuppression, osteoporosis, growth retardation and endocrine dysfunction (e.g. menstrual irregularities, hirsutism, cushingoid state, glucose intolerance, decreased carbohydrate tolerance, increased requirement for insulin or oral hypoglycaemics in patients with diabetes, and secondary adrenocortical, pituitary unresponsiveness). Many of these effects are of special concern during development.

Current place in therapy

MacKay *et al*. [30] and Gupta and Appleton [57] have highlighted the paucity of randomized controlled trials on the use of ACTH and corticosteroids in the treatment of paediatric epilepsies. With respect to the management of infantile spasms, there is evidence that ACTH is effective in the short-term treatment of spasms and in suppressing hypsarrhythmia. In the authors' opinion, ACTH represents the first-line agent for the treatment of infantile spasms, except for spasms associated with tuberous sclerosis. Good results are to be expected within 2 weeks of treatment onset. However, conclusive data supporting the long-term efficacy of ACTH are still lacking in the literature, and there are also inadequate data on the optimal dosage and duration of therapy.

Most authors recommend low-dose synthetic ACTH for a short period, usually less than 6 weeks. In our practice, the treatment protocol for infantile spasms involves use of synthetic ACTH (Synachten Depot®) at a dosage of 2 IU/kg intramuscularly daily for a 14-day period, followed by the same dose every other day for a 14-day period, than every 3 days for a 15-day period. Ranitidine is always associated for gastric protection, and arterial blood pressure is checked before each ACTH injection.

Efficacy results obtained with corticosteroids in infantile spasms appear to be less impressive than with ACTH, but corticosteroids may have advantages in that they can be administered orally and they may have a lower incidence of adverse effects. Prednisone and prednisolone are the most frequently used steroids, at a dosage of 2 mg/kg/day.

The value of ACTH and steroids in other forms of epilepsy, especially late-onset epileptic encephalopathies, is less clearly defined. In these conditions, oral corticosteroids are preferred because they can be used for longer periods, even several months, which allows maintained efficacy over time if a good response is obtained initially. In addition to prednisone and prednisolone, hydrocortisone is frequently prescribed, at an initial dose of 7–8 mg/kg/day, which is gradually decreased afterwards. All patients exposed to long-term corticosteroid treatment should undergo clinical and laboratory assessments at regular intervals to minimize adverse effects related to immunodepression and endocrine dysfunction. Discontinuation of treatment should be done on a gradual basis in order to give the adrenal glands time

to return to their normal pattern of secretion and avoid withdrawal symptoms resulting from the suppression of the hypothalamic–pituitary–adrenal axis.

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33 Benzodiazepines used Primarily for Chronic Treatment (Clobazam, Clonazepam, Clorazepate and Nitrazepam)

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	Clobazam	Clonazepam	Clorazepate	Nitrazepam
Primary indication	First-line and, more often, second- or third-line therapy of partial and generalized seizures (including non-convulsive status epilepticus), as add-on or as monotherapy	*Oral treatment:* second- to third-line therapy of myoclonic seizures, but also other generalized seizures and partial seizures, as add-on or as monotherapy	Second- or third-line therapy of partial and generalized seizures, mostly as add on	Second- to third-line therapy of West syndrome and myoclonic seizures, but also other partial and generalized seizures, mostly as add on
		Intravenous use: second-line therapy for premonitory or early status epilepticus		
Usual preparations	Tablets: 10 mg	Tablets: 0.5 mg, 1 mg, 2 mg	Tablets: 3.75 mg, 7.5 mg, 15 mg	Tablets: 5 mg, 10 mg
	Capsules: 10 mg	Liquid formulation: 1 mg/mL, 2.5 mg/mL		Liquid formulation: 1 mg/mL
Usual dosage	20–40 mg/day in adults; 0.5 mg/kg/day in children	Oral: 0.5–4 mg/day in adults; 0.25–4 mg/day in children	15 mg/day (adults)	5–20 mg/day in adults. In children, treatment may be started at 0.25 mg/kg/day and gradually increased according to response without exceeding 1.5 mg/kg/day and, in any case, 20 mg/day
		Intravenous bolus: 1 mg in adults and 0.1 mg/kg in children, given over 1 min		
Dosing frequency	Once or twice daily	Once or twice daily	Once or twice daily	Once or twice daily
Significant drug interactions	Clobazam clearance is increased by enzyme-inducing agents. Occasionally, clobazam may increase the plasma levels of concomitant antiepileptic drugs	Clonazepam clearance is increased by enzyme-inducing agents	*N*-desmethyldiazepam clearance is increased by enzyme-inducing agents and decreased by cimetidine	Nitrazepam clearance is increased by enzyme-inducing agents
	Co-administration of CNS depressing agents may lead to reciprocal potentiation of adverse effects	Co-administration of CNS-depressing agents may lead to reciprocal potentiation of adverse effects	Co-administration of CNS-depressing agents may lead to reciprocal potentiation of adverse effects	Co-administration of CNS-depressing agents may lead to reciprocal potentiation of adverse effects

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	Clobazam	Clonazepam	Clorazepate	Nitrazepam
Serum level monitoring	Not useful	Not useful	Not useful	Not useful
Target range	Not applicable	Not applicable	Not applicable	Not applicable
Common/ important adverse effects	Sedation, cognitive dysfunction, incoordination, asthenia, mood and behavioural disorders, hypotonia	Sedation, cognitive dysfunction, incoordination, asthenia, mood and behavioural disorders, hypotonia, drooling. With intravenous use, respiratory depression and hypotension	Sedation, cognitive dysfunction, incoordination, asthenia, mood and behavioural disorders, hypotonia	Sedation, cognitive dysfunction, incoordination, asthenia, mood and behavioural disorders, hypotonia, drooling
Main advantages	Broad-spectrum activity against many seizure types, high responder rates, less sedating than other benzodiazepines	Broad-spectrum activity against many seizure types	Broad-spectrum activity against many seizure types	Broad-spectrum activity against many seizure types
Main disadvantages	Tolerance and withdrawal seizures limit clinical usefulness	Tolerance and withdrawal seizures limit clinical usefulness	Few clinical data in epilepsy. Tolerance and withdrawal seizures limit clinical value	Tolerance and withdrawal seizures limit clinical usefulness
Mechanism of action	Potentiation of $GABA_A$-mediated inhibition	Potentiation of $GABA_A$-mediated inhibition	Potentiation of $GABA_A$-mediated inhibition	Potentiation of $GABA_A$-mediated inhibition
Oral bioavailability	>90%	>85%	>90%	>80%
Time to peak levels after oral dose	0.5–2 h	1–4 h	0.5–2 h[a]	1.3–2.5 h
Metabolism and excretion	*N*-demethylation and hydroxylation	Nitroreduction, acetylation and hydroxylation	Decarboxylation, glucuronidation, hydroxylation	Nitroreduction, acetylation and hydroxylation
Volume of distribution	0.9–1.8 L/kg	1.5–4.4 L/kg	0.7–2.2 L/kg[a]	2.5–2.9 L/kg
Elimination half-life	10–30 h for clobazam; 35–45 h for *N*-desmethylclobazam	17–55 h	40–130 h[a]	20–40 h
Plasma clearance	0.36–0.63 mL/min/kg	1.56–2.10 mL/min/kg	0.18–0.27 mL/min/kg[a]	1.51–1.91 mL/min/kg
Protein binding	85–90%	86%	96–98%	85–88%
Active metabolites	*N*-desmethylclobazam	None	*N*-desmethyldiazepam	None
Comment	The most useful benzodiazepine for chronic treatment, due to broad-spectrum activity, relatively high response rates in refractory epilepsy, and relatively good tolerability. Valuable for short-term use in periods of seizure exacerbation. May be an option for initial monotherapy in selected patients. Tolerance and withdrawal seizures represent main drawbacks	Used mainly as a second- and third-line option for the long-term treatment of myoclonic seizures, particularly in children, but can be useful in many other seizure types. Use in serial seizures and status epilepticus has fallen gradually out of favour, having been largely superseded by midazolam, lorazepam and diazepam. Tolerance, withdrawal seizures and, in children, drooling represent significant drawbacks	It is the least well-documented benzodiazepine for use in epilepsy, and it is rarely prescribed today	It is used almost exclusively in children, as a third-line add-on treatment for West syndrome and some symptomatic generalized epilepsies. Tolerance, withdrawal seizures and, in children, drooling represent significant drawbacks

CNS, central nervous system.

[a] Clorazepate is rapidly and completely decarboxylated in the stomach to *N*-desmethyldiazepam and therefore reported pharmacokinetic parameters refer to *N*-desmethyldiazepam.

Introduction

Benzodiazepines were initially developed for the treatment of anxiety, with chlordiazepoxide first marketed in about 1960. By 1965, diazepam was demonstrated to be efficacious in the treatment of status epilepticus. Chronic use of benzodiazepines in epilepsy was introduced in the early 1970s, when clonazepam, clorazepate and nitrazepam became available. Somnolence and behavioural changes were commonly associated with these benzodiazepines. Clobazam, introduced in the late 1970s, seemed to have less sedative effects than other benzodiazepines, and in 1978 Gastaut first reported its value in epilepsy treatment [1].

The benzodiazepines discussed in this chapter (clobazam, clonazepam, clorazepate and nitrazepam) are all used for the daily, chronic treatment of epilepsy in children and adults. Benzodiazepines used for emergency treatment are discussed in Chapter 34.

Clobazam is not yet licensed for the treatment of epilepsy in the USA, but is used widely in most of the rest of the world, especially in Canada [2–3]. Clonazepam is the benzodiazepine most commonly used in epilepsy treatment in many countries, while nitrazepam is used less often. Clorazepate is the least well-documented benzodiazepine for use in epilepsy and probably it is the least frequently prescribed.

Significant behavioural adverse effects have legitimately limited the use of these medications in the current treatment of epilepsy. Concerns about tolerance have been widely communicated, although this issue has not been adequately defined in studies conducted to date. In general, benzodiazepines have been relegated to second-line agents, with the possible exception of clobazam. However, they are very potent medications and may offer remarkable relief in a variety of syndromes and in most seizure types.

There are no randomized clinical trials that have compared clobazam, clonazepam, clorazepate and nitrazepam. Therefore, comments about the utility of one over the other are not evidence based and spring from clinical impression and case series.

Chemistry

All benzodiazepines are made up by the combination of a benzene ring with a diazepine ring with the nitrogen in the heterocyclic ring in the 1–4 position for clonazepam, clorazepate and nitrazepam, while clobazam has a 1–5 ring structure [4].

Clobazam (8-chloro-5-methyl-1-phenyl-1,5-benzodiazepine-2,4-dione; $C_{16}H_{13}ClN_2O_2$) is a crystalline powder with a molecular weight of 301, relatively insoluble in water; clonazepam [5-(2-chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one;$C_{15}H_{10}ClN_3O_3$] is a light-yellow crystalline powder with a molecular weight of 315.7; clorazepate (7-chloro-2-oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepine-3-carboxylic acid; $C_{16}H_{11}ClN_2O_3$) is an off-white to pale yellow crystalline powder with a molecular weight of 408.9, relatively soluble in water (100–200 mg/mL); and nitrazepam (7-nitro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one; $C_{15}H_{11}N_3O_3$) is a yellow crystalline powder with a molecular weight of 281.3, insoluble in water. Figure 33.1 shows the specific chemical structure of each drug.

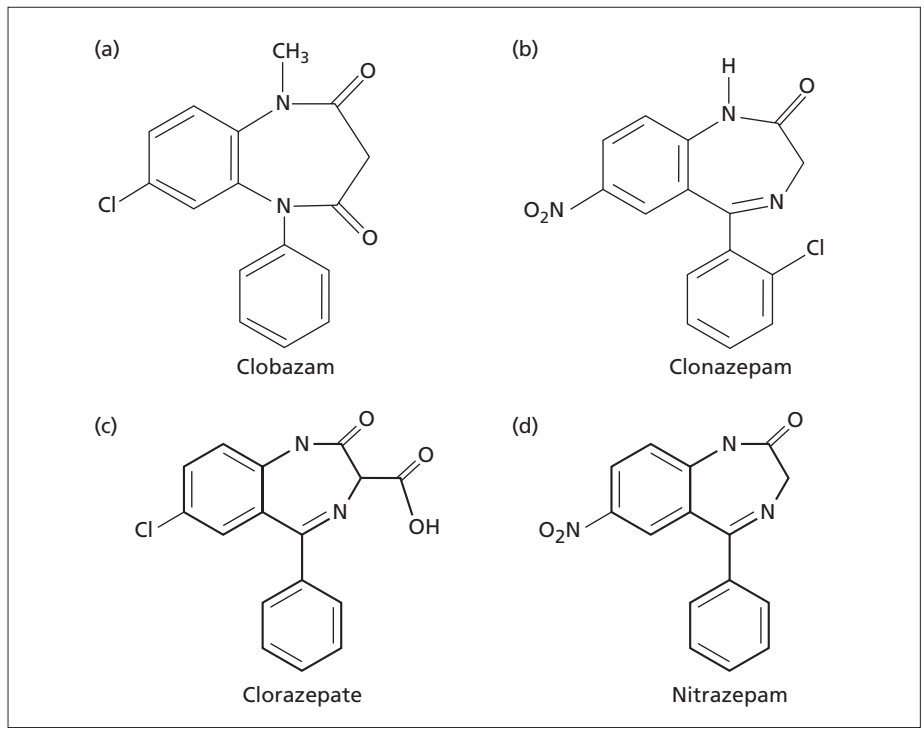

Fig. 33.1 Structures of the major compounds presented in this chapter.

Mechanism of action

All benzodiazepines are thought to exert their primary effects by binding to specific modulatory sites (the so-called benzodiazepine receptors) at the γ-aminobutyric acid (GABA) type A receptor–chloride channel complex [5]. They appear to increase the effect of GABA at the $GABA_A$ receptor by increasing the affinity of GABA for the receptor and by potentiating the response triggered by GABA binding to the receptor. This results in greater chloride influx mediated by an increased frequency of chloride channel openings, rather than by changes in channel opening time. Benzodiazepines bind at a different site from GABA – so their effect is to enhance the effects of GABA.

The $GABA_A$ receptor complex includes multiple subunits made up from 19 polypeptides in various combinations. Different subunit combinations have been further characterized. For example, the α-1-containing benzodiazepine receptor site may mediate the anxiolytic effect, the α-2 the sedation effect, the α-3 muscle relaxation and α-5 the cognitive effects [6]. The differing effects of various benzodiazepines may be related to differential binding to these subunits.

Pharmacokinetics

The main pharmacokinetic parameters of clobazam, clonazepam, clorazepate and nitrazepam are summarized in the table at the beginning of this chapter.

Absorption

Benzodiazepines are readily absorbed from the gastrointestinal tract, peak serum concentrations usually being attained in less than 4 h after a single oral dose. In the case of clorazepate, absorption is preceded by rapid decarboxylation in the acidic medium of the stomach to the active product *N*-desmethyldiazepam, for which clorazepate can be considered a prodrug. The oral bioavailability of clobazam, clonazepam, clorazepate (expressed in terms of *N*-desmethydiazepam equivalents) and nitrazepam is almost complete.

Distribution

Most benzodiazepines, including clobazam and its active *N*-desmethyl metabolite, clonazepam, clorazepate-derived *N*-desmethyldiazepam and nitrazepam, are extensively bound to plasma proteins. All these compounds are lipophilic and readily cross the blood–brain barrier, resulting in a rapid onset of action. Apparent volumes of distribution are in excess of 1 L/kg, indicating extensive penetration into tissues.

Elimination

Benzodiazepines are eliminated almost entirely by metabolism. Clobazam is cleared by *N*-demethylation and hydroxylation, clonazepam by nitroreduction, acetylation and hydroxylation, *N*-desmethyldiazepam (derived from clorazepate) by glucuronidation and hydroxylation, and nitrazepam by nitroreduction, acetylation and hydroxylation. Clobazam is converted to the active metabolite *N*-desmethylclobazam, whereas clorazepate is a prodrug for *N*-desmethyldiazepam. Elimination half-lives in non-induced healthy adults are in the order of 10–50 h for clobazam (35–45 h for *N*-desmethylclobazam), 17–55 h for clonazepam, 40–130 h for *N*-desmethyldiazepam and 20–40 h for nitrazepam. Studies in elderly patients have demonstrated that in old age the clearance of clobazam and *N*-desmethyldiazepam is decreased and half-life is increased, much more so in men than in women.

Drug interactions

The clearance of clobazam, clonazepam, *N*-desmethyldiazepam and nitrazepam is increased by concomitant treatment with enzyme-inducing agents. In the case of clobazam, this effect is associated with increased plasma levels of the active *N*-desmethyl metabolite.

Benzodiazepines generally have no major effects on the pharmacokinetics of concurrently administered drugs [7]. However, a few reports have suggested that in occasional patients clobazam may increase the plasma concentration of phenytoin, carbamazepine, carbamazepine-10,11-epoxide and valproic acid. Reports also suggest that, in rare cases, co-administration of benzodiazepines with valproic acid may result in reciprocal potentiation of their effects, and sometimes in encephalopathic symptoms. A pharmacodynamic interaction resulting in reciprocal potentiation of adverse effects may occur when benzodiazepines are co-administered with alcohol or other central nervous system (CNS) depressants.

Serum level monitoring

There is a large variation in the serum concentrations of benzodiazepines at which therapeutic and toxic effects occur. In general, dose adjustments are guided by observation of clinical response and measuring serum drug levels is of little or no value in the individualization of therapy.

Efficacy

The paucity of randomized clinical trials with benzodiazepines makes their role in chronic epilepsy treatment uncertain. Most studies have examined their use as an 'add-on' medication and not as initial therapy.

Clobazam

Clobazam has been reasonably well demonstrated to have efficacy against many seizure types as an add-on drug in children and adults [8]. In addition, in children it can be considered for first-line monotherapy [8].

In a large open-label, retrospective Canadian study, clobazam was reported to be efficacious against all seizure types in 877 patients, 51% of whom were children [9]. There were excellent responses in partial, secondary generalized, absence, akinetic and myoclonic seizures. All patients had failed one or more antiepileptic drugs (AEDs) before the introduction of clobazam, and based on survival analysis it appeared that 40% continued to receive clobazam 4 years later. This may reflect excellent efficacy,

or physicians' inertia in making therapeutic adjustments. A variety of smaller open-label studies in adults and children have reached similar conclusions.

Double-blind studies have shown definite efficacy for clobazam in partial seizures in children and adults as an add-on treatment [10,11]. The value of clobazam in refractory epilepsy has been examined in four blinded cross-over trials with a total of 196 patients, both children and adults. A recent Cochrane review concluded that 'clobazam as an add-on treatment may reduce seizure frequency and may be most effective in partial-onset seizures. However, it is not clear who will best benefit and over what time-frame' [12]. The largest of the clobazam double-blind cross-over trials involved 129 adults, mainly with resistant partial-onset seizures, and involved 12 weeks on active medication and 12 weeks on placebo [10]. The average dose of clobazam was estimated to be about 0.17–0.67 mg/kg/day. Overall, the number of seizures was significantly reduced with clobazam and 19 (15%) patients achieved seizure freedom compared with no seizure-free patients on placebo.

Clobazam has been studied as monotherapy in a Canadian study in 235 children with recent-onset partial, secondary generalized and generalized tonic–clonic seizures [8]. This study used a double-blind, double-dummy placebo design and compared clobazam ($n = 119$) with carbamazepine ($n = 78$) and phenytoin ($n = 38$) in children with newly treated epilepsy ($n = 115$) or after the failure of a first AED ($n = 120$). When the patient entered the study, the initial dose escalation was by protocol over 1–3 weeks to achieve clobazam 0.5 mg/kg/day, carbamazepine 10 mg/kg/day and phenytoin 5 mg/kg/day. Thereafter, physicians could adjust the dose as dictated by the clinical situation, including serum drug levels, but the double-dummy technique maintained the blind throughout the study. Analysis was by intention to treat and the primary endpoint was retention on the initial drug for 12 months, a measure that balances efficacy with side-effects and mimics clinical practice. Compliance was excellent and 92% of patients received ≥95% of their doses. Overall, 56% were retained on their initial drug and there was no statistical difference between clobazam and the other two medications. The rate of adverse effects leading to discontinuation of the study drug was the same for all three drugs, and seizure control was virtually identical. As noted below, 'tolerance' was no more frequent with clobazam than with the other two AEDs. Therefore, at least in children, monotherapy with clobazam has good efficacy in newly treated patients or those who have failed a first AED.

Clobazam has been studied in several special circumstances. An open-label, randomized trial compared clobazam with phenytoin in 48 patients with seizures from cysticercus granulomas [13]. Outcome was assessed after 6 months and clobazam, at a dose of 0.5 mg/kg/day, was more effective than phenytoin ($P = 0.03$).

In febrile seizures, a carefully orchestrated, double-blind trial compared intermittent clobazam administered for 48 h at the time of illness (≤5 kg body weight: 5 mg/day; 6–10 kg: 5 mg twice daily; 11–15 kg: 7.5 mg twice daily; >15 kg: 10 mg twice daily) in 19 patients with placebo in 20 patients. Recurrent febrile seizures occurred in 12.5% of subsequent febrile illnesses with placebo but in only 1.7% with clobazam ($P = 0.01$). There are many pitfalls in the intermittent treatment for febrile seizures, but if such an approach is taken, clobazam may be a reasonable option because it seems to be fairly well tolerated and not particularly sedating at a dose of about 0.5 mg/kg/day [14].

Clobazam has a quick effect on seizure control which has led to its use in catamenial epilepsy [15]. A double-blind study compared 20–30 mg of clobazam/day versus placebo in 18 women with catamenial epilepsy. The treatments were administered for the 10 days that overlapped their menses, and in 14 women clobazam was superior to placebo, usually suppressing all seizures. It has also been suggested that clobazam can provide short-term additional therapeutic cover during periods of increased seizure frequency or when patients are considered at special risk for seizure exacerbation, for example during a switch from one AED to another or for overnight travel [16,17].

Oral clobazam has also been reported to be effective in non-convulsive status in several open-label, clinical case series. In one study, 16 patients (six with absence status, one with myoclonic absence status, one with tonic status and seven with simple or partial complex partial status) were given clobazam as a single oral dose of 0.5–1.7 mg/kg with apparent complete success within 25 minutes in 15 of 16 [18]. Another study involved four adult patients with complex partial status whose seizures had failed to respond to intravenous phenytoin plus lorazepam, diazepam or midazolam [19]. Clobazam was given as a single oral dose of 60 or 70 mg, with prompt cessation of seizures with electroencephalogram (EEG) documentation.

Clonazepam

There is no doubt that clonazepam has significant efficacy for most seizure types and epilepsy syndromes although currently it is used infrequently as initial therapy because there are alternatives with fewer adverse effects [20]. Clonazepam was introduced for the treatment of epilepsy when rigorous, randomized, double-blind trials were not always required for drug registration and there are no randomized studies with a large enough sample size to indicate if clonazepam is equivalent to, or superior to, any other drug.

There is, however, a strong perception that clonazepam is particularly effective for myoclonic seizures in patients with cryptogenic and symptomatic generalized epilepsy syndromes, including progressive myoclonic epilepsies [21,22]. Based on open-label studies or small randomized trials, there is evidence that clonazepam is effective in other generalized seizure types including absence, atonic/akinetic seizures and tonic seizures [23,24]. In support of its value in absence, Browne [23] noted at least 34 published clinical series, all of which describe a 'favorable response'. Open-label, uncontrolled studies have also suggested that clonazepam may be effective in West syndrome and progressive myoclonic epilepsies [21,25]. Cryptogenic and symptomatic generalized epilepsy syndromes are typically characterized by multiple generalized seizure types. In 1975, Carson and Gilden [26] described their experience with 52 such children followed for a mean of 15 months. Clonazepam was added to their drug regime and 27% had complete seizure control while 61% had >50% reduction in seizures. Only 10% had no improvement [26].

Clonazepam also has efficacy in partial seizures in adults [27]. Several small randomized add-on studies for refractory patients and open-label studies have suggested substantial efficacy in temporal lobe epilepsy and simple partial seizures [23,24]. A

randomized trial of 36 adults with newly treated complex partial seizures suggested that monotherapy with clonazepam was equally as effective as carbamazepine at conventional doses, although this trial was clearly underpowered to prove equivalency [28].

Intravenous clonazepam is available for the treatment of status epilepticus in many countries but not in the USA. Clonazepam is thought to have a longer duration of action (~24 h) than diazepam (~2 h) but a shorter duration of action than lorazepam (up to 72 h); however, no randomized trials in status epilepticus have compared clonazepam with other benzodiazepines or any other medications. In small open-label trials, clonazepam appears to be effective in convulsive status epilepticus, absence status and partial status [23]. In the earliest study, Gastaut successfully treated eight children and 28 adults with status epilepticus with a 'slow' intravenous infusion of clonazepam (slow was not defined) [29]. One additional adult did not respond. Twenty-five patients were successfully treated with 1 mg, but others received up to 8 mg. The response was often within a minute of infusion [29]. In the next published study there were 17 episodes of status in 17 children treated with 0.01–0.09 mg/kg clonazepam as an intravenous bolus [30]. There was an initial complete cessation of seizures in all; however, in six, the seizures recurred from ~1 h to 24 h later. There were no 'serious side effects' other than drowsiness. In an additional study, intravenous clonazepam was successful in 7 of 7 patients with absence status, 7 of 14 with convulsive status and 2 of 3 with partial complex status [31].

Based on these and other studies it appears that, if clonazepam is used for status epilepticus, an initial bolus dose of 0.1 mg/kg is appropriate for children and an initial bolus dose of 1.0 mg is appropriate for adults.

Clorazepate

Clorazepate has mostly been reported as effective in short-term experiences in patients with refractory epilepsy. Its use in specific epilepsy syndromes has not been clearly assessed, as clorazepate was introduced in an era when syndromes were not clearly delineated. There is only one published double-blind, cross-over trial in adults that compared clorazepate with phenobarbital in 42 patients who were simultaneously treated with phenytoin [32]. All patients had partial seizures with or without secondary generalization. The analysis was not by intention to treat and there were a substantial number of drop-outs. There was little difference in the rate of seizure control, although physicians suggested that the clorazepate–phenytoin combination was superior based on a judgement that combined seizure control with tolerability.

All studies of chlorazepate in children have been open-label, small (<20 subjects) and without blinded or objective outcomes. The drug appears to have some effect on akinetic, absence, myoclonus and generalized tonic–clonic seizures [33,34].

Nitrazepam

There are fewer publications about nitrazepam than about clonazepam and clobazam. Most of the studies have focused on patients with severe, AED-resistant cryptogenic and symptomatic generalized epilepsies. Nitrazepam has been described as effective for myoclonic, atonic and atypical absence seizures and seems to have a significant effect in West syndrome [3]. One complex and not completely definitive trial randomized 52 children with infantile spasms to nitrazepam or adrenocorticotropic hormone (ACTH) for a 4-week course [35]. Most patients had failed previous treatments for West syndrome; however, both drugs appeared to be equally efficacious in terms of per cent reduction of spasms compared with baseline (75% had >50% reduction). Few patients became seizure free and ACTH appeared to have more serious adverse effects.

In a series of small open-label, retrospective trials, nitrazepam seemed to be effective in a variety of childhood-onset epilepsy syndromes, including Lennox–Gastaut syndrome [36,37]. One study reported 12 children with drug-resistant Lennox–Gastaut syndrome who were treated with a median dose of nitrazepam 1.5 mg/kg/day for 13–30 months. The response was modest: two became seizure free for 1.5–2 years, five had >50% reduction in seizure frequency and six had >25% reduction [37].

Tolerance

Tolerance has been noted with all benzodiazepines, with most of the relevant literature in animal studies [38,39]. The concept of tolerance is that after seizure control has been achieved with a given dose of a medication, re-emergence of seizures may occur gradually over time, and seizure frequency may eventually return to the original level. A dose increase may lead again to seizure control, again followed by a return of seizures. There are remarkably few clinical studies that demonstrate the true incidence and significance of this problem and even fewer that compare tolerance with a given benzodiazepine and any other AED. In most studies, tolerance is not clearly defined and there is no consensus about a quantitative definition. How long does the patient need to be seizure free before tolerance can occur, and at what dose? If a patient becomes only partially seizure free, can tolerance develop? If seizures are controlled with an increased dose, does this equate to tolerance? The large Canadian retrospective study of refractory epilepsy patients suggested that 9% of patients discontinued clobazam because of tolerance. The definition of tolerance was left to the discretion of the treating physician [9].

In a randomized, double-blind study of clobazam versus carbamazepine versus phenytoin in children with recently diagnosed epilepsy, we suggested that tolerance occurred when a child was seizure free for 3–6 months and then had sufficient seizures that the medication was considered a failure [9]. In this study, tolerance developed in 7.5% of patients receiving clobazam, 4.2% receiving carbamazepine and 6.7% receiving phenytoin (P = no significance). Of all patients randomized to clobazam, 23% were seizure free for the entire year of the study, which is identical to the 25% randomized to carbamazepine but superior to the 11% on phenytoin. As the study duration was 1 year for each patient, tolerance developing later in the clinical course could not be assessed.

Studies of adults with resistant temporal lobe epilepsy have not been so optimistic. When clobazam was added to their regime, a large percentage had a greatly improved seizure control, but then many lost this control over the next few weeks or

months [40,41]. Schmidt suggested that in adults with refractory partial seizures treated with clobazam, 40% had at least a 75% reduction in seizures [11,42]. This was based on a double-blind add-on study of only 20 patients with refractory complex partial seizures who were treated for 3 months. Tolerance was suggested in 56%.

What may separate benzodiazepines from other AEDs in refractory patients is the relatively high rate of initial response. The long-term response rate appears to be equivalent to, or better than, that associated with most other medications used in patients who already failed several other AEDs. The study of Singh *et al*. [40] illustrates this. Clobazam was introduced in 173 adults with uncontrolled epilepsy and 50 (29%) had a good response (>75% reduction in seizure frequency) for at least a month. Over the next 3 years (average follow-up), 25 (14%) retained their good response while 25 (14%) developed 'tolerance' in the sense that seizure frequency increased back to no better than 50% of their baseline pre-clobazam state. Tolerance developed after a mean interval of 8.9 ± 7.9 months but it is of interest that 56% of those with tolerance continued with the drug, suggesting that there was some benefit but just not as much as the initial response. Another way of looking at these data is that 50% of responders maintained their response for 3 years or longer.

Adverse effects

Benzodiazepines have significant adverse effects and careful clinical monitoring is important, particularly shortly after starting a new medication. Much of the literature about the adverse effects of benzodiazepines comes from studies of patients who received the drugs for non-epilepsy indications such as anxiety disorders, and few of the observations in patients with epilepsy are based on blinded trials. There are few randomized trials that have compared one benzodiazepine with another, or a given benzodiazepine with other medications.

To varying degrees, all benzodiazepine drugs may cause sedation, cognitive dysfunction, unsteady gait and behavioural/personality changes. The authoritative review of clonazepam by Browne [23] suggested that drowsiness was noted in 3–85% of treated patients and ataxia in 4–79%. These astonishingly wide estimates may be the result of varying rates of dose escalation, total daily dose and methodology used to assess adverse effects. Many authors have noted that somnolence and ataxia are noted most often early in the treatment and tend to be less of a problem over time. It has been very challenging to separate the effects of sedation from effects on cognition.

Particularly in children, there may be 'paradoxical' hyperactivity, irritability or aggression. Again, Brown [23] notes a wide range in frequency – from 2% to 52%! The severity of this problem ranges from mild to catastrophic. Disinhibition problems may be less problematic in adults. In a retrospective review of 323 adult patients hospitalized with psychiatric disorders, externalizing behaviour problems such as aggression or need for restraints were no more common with or without benzodiazepine use [43]. Particular concern has been expressed about recognition of behavioural side-effects in people with mental handicap, because epilepsy in this population is often complex with multiple seizure types for which benzodiazepines are a logical choice [44].

In adults, depression has been noted in about 10% of patients starting clonazepam [45]. The symptoms of depression are typically noted as soon as the drug is introduced and may resolve with dose reduction.

Sexual dysfunction in adults has been noted in a few patients, including anorgasmia, ejaculatory inhibition, decreased libido and difficulty achieving orgasm or maintaining erections [45]. It is unclear how often these effects are an issue.

When elderly people are prescribed benzodiazepines for anxiety or sleep problems, there is a doubling of the risk of 'injurious falls' and fractures [46]. It is not clear if all benzodiazepines are associated with the same level of risk.

A special concern in children and in people with significant bulbar problems is an exacerbation of swallowing problems with increased drooling and aspiration pneumonia. These issues are particularly prominent with nitrazepam and clonazepam [23,47].

Withdrawal of benzodiazepines in people with epilepsy may lead to benzodiazepine withdrawal symptoms and increased seizures. Benzodiazepine withdrawal symptoms, apart from seizures, most often include insomnia, agitation and confusion [48]. These symptoms have a sudden onset if the drug withdrawal is abrupt and can typically be avoided by slowly tapering the medication. The definition of 'slow' is unclear but probably is many weeks. Chronic use of benzodiazepines is also associated with a risk of withdrawal seizures (including status epilepticus) following dose reduction or discontinuation, particularly when a fast discontinuation rate is used and even in patients in whom the medications did not seem to have an effect on seizure frequency. No randomized trials have addressed this clinical observation. Several small studies suggest that about 30% of children who have been treated with clonazepam will have exacerbations of their seizures when the drug is withdrawn [49,50]. There is no clearly safe rate of discontinuation to avoid this problem, even with rates as slow as 0.04 mg/kg/week [50].

Benzodiazepines do not appear to be significant teratogens [51]. High-dose benzodiazepine use in pregnancy has typically been associated with the use of other medications or alcohol abuse, which makes the study of benzodiazepine-induced fetal anomalies difficult. At modest doses, benzodiazepines are not associated with an increased risk of malformations. There may be withdrawal symptoms in the infant but benzodiazepines do not appear to have pervasive effects on the long-term behavioural or cognitive outcome of children exposed prenatally. All of the benzodiazepines used in the treatment of epilepsy are excreted into breast milk; however, the levels are low and breastfeeding is not contraindicated.

Clobazam

Clobazam appears to be the best tolerated of the four drugs [1]. In the paediatric Canadian double-blind trial, clobazam showed marginal increases over carbamazepine and phenytoin in the frequency of externalizing behaviour problems [8] based on a symptom checklist administered at each follow-up visit. There was no difference in cognitive effects over a year of treatment

based on an extensive battery of neuropsychological tests [52]. Overall, potential side-effects such as somnolence or ataxia were equal between the three drugs.

Clonazepam

Personality and behavioural changes in children treated with clonazepam have been especially prominent. The frequency of these manifestations is not easily judged and in open-label studies has varied tremendously, from 2% to 50% [23]. Children have been described as 'difficult', hyperactive, aggressive, irritable or violent. For some patients, these behavioural reactions seem dose related, and there is some evidence for tolerance developing over time; however, for many children, these effects are apparent at small doses and clinically unacceptable.

Drowsiness seems to occur in about 30% of adults and ataxia occurs to a similar degree [23]. These symptoms have been observed to be most prominent in the first few days or weeks of treatment and may improve with dose reduction and the passage of time. There is no randomized study that establishes this clinical observation. Overall, it has been suggested that about 20% of patients have intolerable adverse effects requiring discontinuation of the drug [23].

Intravenous clonazepam has the potential to induce respiratory failure, similar to diazepam. The frequency of this effect is unclear from the published literature but it appears to be rare. It is almost certainly related to the dose and rapidity of infusion, but neither is clearly defined. As mentioned above, an initial bolus of 0.01 mg/kg for children or 1 mg for adults appears safe [29–31].

Clorazepate

Since clorazepate is rapidly converted to desmethyldiazepam, it is not surprising that somnolence has been reported frequently [53]. There is only a single, published, randomized trial that has compared clorazepate with phenobarbital in adults with resistant epilepsy [32]. Clorazepate had somewhat less 'toxicity' based on a non-standardized scoring system that included a variety of symptoms ranging from sleepiness to 'grossly impaired coordination'.

Nitrazepam

Nitrazepam has been associated with a high rate of bulbar dysfunction manifested by drooling, coughing, gagging and difficulty swallowing. Increased drooling is often blamed on increased secretions; however, the mechanism of this problem has been clearly shown to be swallowing discoordination [47]. At higher doses of nitrazepam, there have been several documented deaths in children with pre-existing swallowing problems, which has led to a recommendation not to exceed a daily dose of 1 mg/kg/day [54].

Place in current therapy

It is challenging to define the optimal role for benzodiazepines in the current treatment of epilepsy. In our opinion clobazam is the "star" of the group with many possible indications. Clonazepam remains a useful second-line medication. Nitrazepam has a limited role for special patients only, and clorazepate has no clear indications.

In childhood, clobazam monotherapy can be used as first-line treatment for nearly all epilepsy syndromes, with a few important exceptions. Without any supporting data, we prefer valproic acid as a first-choice AED for all idiopathic generalized epilepsies except for benign myoclonic epilepsy of infancy, where clobazam is a better tolerated first choice. Among cryptogenic and symptomatic generalized epilepsies, ACTH and vigabatrin are better choices for West syndrome, and valproic acid remains our first choice for myoclonic astatic epilepsy.

The paediatric syndromes for which we routinely use clobazam as initial monotherapy are benign myoclonic epilepsy of infancy, most unspecified cryptogenic and symptomatic generalized epilepsies, and idiopathic, symptomatic and cryptogenic partial epilepsies. The reasons to choose clobazam are its excellent, rapid efficacy and virtually no risk of serious adverse effects. We select patients with normal behaviour and tend to use other medications when there are pre-existing externalizing behaviour problems, for fear that these will be exacerbated by clobazam. Another indication for clobazam is as initial treatment immediately after the diagnosis of epilepsy, until the work-up is completed. We start with a dose of about 0.25 mg/kg/day and increase over a few weeks to 0.5 mg/kg/day. If seizure control is unsatisfactory we increase the dose up to about 1.5 mg/kg/day but do not usually go beyond this dose – our experience includes few responders at higher doses.

When a drug other than clobazam has failed in children, then clobazam can be considered for nearly all syndromes as an add-on. It can also be used as a very helpful 'bridge' when the up-titration of another drug is very slow, for example with lamotrigine.

In adults, clobazam as initial monotherapy has not been well studied and we suggest that it is considered as a second or third alternative. Because it has nearly no drug interactions, it can be added to any AED, with the option of withdrawing the pre-existing medication slowly. All types of adult-onset epilepsy may respond to clobazam.

Clonazepam is a less successful benzodiazepine than clobazam because of its adverse effects, including behavioural problems, somnolence and ataxia. It should be considered strongly for adults and children when myoclonus or other generalized seizures have failed to respond to other first-line medications. Even though clonazepam has efficacy against partial seizures, we rarely use it for this group of patients because there is a wealth of alternatives with fewer adverse effects. We introduce clonazepam very slowly, starting with approximately 0.025 mg/kg/day and gradually increase the dose to the range of 0.1 mg/kg/day.

For status epilepticus, we use lorazepam, diazepam or midazolam because intravenous clonazepam is not readily available in our country. We are aware of a number of centres in Europe that preferentially use intravenous clonazepam for status, apparently with good effect.

Nitrazepam is a powerful medication, in terms of both efficacy and adverse effects. Somnolence, drooling and swallowing problems limit its use, although in our experience it has sometimes been remarkably effective. Patients with resistant West syndrome or other cryptogenic or symptomatic generalized epilepsies are

good candidates for nitrazepam when several other medications have failed. We rarely use nitrazepam in patients with swallowing difficulties. There is little experience with nitrazepam in adults to guide its use.

Finally, there is an interesting issue when a first benzodiazepine has failed – is there any value in attempting treatment with an alternative? When clonazepam or nitrazepam has failed because of adverse effects, we will often substitute clobazam. If clobazam fails for reasons of efficacy and there are few other medication alternatives, we may attempt treatment with clonazepam or nitrazepam, occasionally with gratifying results.

Benzodiazepines should continue to be used for the treatment of epilepsy in children and adults, but the importance of careful clinical monitoring for adverse effects should be emphasized.

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34 Benzodiazepines used Primarily for Emergency Treatment (Diazepam, Lorazepam and Midazolam)

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	Diazepam	Lorazepam	Midazolam
Primary indication	*Adults and children:* premonitory and early status epilepticus, serial seizures, acute symptomatic seizures	*Adults and children:* premonitory and early status epilepticus (preferred drug in stage 1 of status epilepticus), serial seizures, acute symptomatic seizures	*Adults, continuous infusion:* refractory status epilepticus *Children, buccal, or intranasal route:* premonitory and early status epilepticus, serial seizures, acute symptomatic seizures
Usual preparations	Vials: 5 mg/mL, 10 mg/mL Rectal gel: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg Rectal tubes: 5 mg, 10 mg Capsules: 2 mg, 5 mg Tablets: 2 mg, 5 mg, 10 mg Oral drops: 5 mg/mL	Vials: 2 mg/mL, 4 mg/mL Tablets: 0.5 mg, 1 mg, 2 mg, 2.5 mg Oral drops: 1 mg/mL	Vials: 1 mg/mL, 5 mg/mL Tablets: 7.5 mg, 15 mg
Usual dosage	Intravenous bolus: 10–20 mg (adults); 0.2–0.3 mg/kg (children), usual injection rate 2–5 mg/min (adults and children), strictly intravenously Rectal: 20–30 mg (adults); 0.5–0.75 mg/kg (children) Intramuscular, intranasal: not recommended	Intravenous bolus: 4–8 mg (adults); 0.1 mg/kg (children), strictly intravenously, usual injection rate 2 mg/min (adults and children)	Intravenous infusion: 0.1–0.3 mg/kg bolus at 4 mg/min (adults and children), followed by infusion at 0.05–0.4 mg/kg/h (adults) Paediatric initial infusion rates are 0.03 mg/kg/h in newborns of gestational age <32 weeks; 0.06 mg/kg/h in newborns of gestational age >32 weeks and in infants <6 months; and 0.05–0.12 mg/kg/h in children >6 months. These rates may be increased according to response Higher infusion rates have been used (and may be required), both in adults and in paediatric patients Intranasal or buccal: 5–10 mg (adults); 0.15–0.3 mg/kg (children)
Significant drug interactions	Diazepam clearance is increased by enzyme inducers and decreased by inhibitors of CYP3A4 (e.g. cimetidine, erythromycin, itraconazole) and CYP2C19 (e.g. fluvoxamine, omeprazole). Diazepam and other central nervous system depressants may potentiate reciprocally their actions when administered together	Lorazepam clearance is increased by enzyme inducers and decreased by valproic acid. Lorazepam and other CNS depressants may potentiate reciprocally their actions when administered together	Midazolam clearance is increased by enzyme inducers and decreased by CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, diltiazem, verapamil or cimetidine. Midazolam and other CNS depressants may potentiate reciprocally their actions when administered together

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	Diazepam	Lorazepam	Midazolam
Serum level monitoring	Not useful	Not useful	Not useful
Target range	Not applicable	Not applicable	Not applicable
Common/important adverse effects	Sedation, respiratory depression, hypotension, injection site reactions	Sedation, respiratory depression, hypotension, injection site reactions	Sedation, respiratory depression, hypotension
Main advantages	Rapid onset of action with the intravenous route Rectal formulation available Long-standing clinical experience in adults and children Widespread availability	Rapid onset of action by the intravenous route Long-lasting effect (>24 h) after a single injection Proven efficacy in randomized controlled trials in generalized tonic–clonic status epilepticus Long-standing clinical experience in adults and children	Water solubility permits alternative routes in the emergency treatment of seizures. Buccal and intranasal routes have proven efficacy in randomized controlled trials in children with acute seizures Rapid onset of action with all routes Intranasal and buccal routes easy and socially well accepted Lack of reactions at the infusion site Little risk of accumulation
Main disadvantages	Short duration of action due to rapid redistribution Accumulation after repeated doses and infusion, with the risk of prolonged sedation and respiratory depression Adverse effects from the polypropylene solvent	Rapid development of tolerance Adverse effects from the polypropylene solvent	Short duration of action with risk of seizure relapse
Mechanism of action	Potentiation of $GABA_A$ receptor-mediated inhibition	Potentiation of $GABA_A$ receptor-mediated inhibition	Potentiation of $GABA_A$ receptor-mediated inhibition
Bioavailability	Oral: 100 ± 14% Rectal: 80–100%	Oral: 93 ± 10%	Oral: 44 ± 17% Intramuscular: 91% Intranasal: 83 ± 19% Buccal: 74.5%
Time to peak levels after single dose	Intravenous: 3–15 min, injection rate 2–5 mg/min Rectal: 3–30 min	Intravenous: 1–5 min; injection rate 2 mg/min	Intravenous: 1–5 min; injection rate 1 mg/kg/min Intramuscular: 20–30 min Intranasal: 10–15 min Buccal: 15–90 min
Main routes of elimination	Oxidative demethylation	Glucuronidation	Oxidation
Volume of distribution	1.1 ± 0.3 L/kg	1.3 ± 0.2 L/kg	1.1 ± 0.6 L/kg
Elimination half-life	43 ± 13 h	14 ± 5 h	1.9 ± 0.6 h
Plasma clearance	0.38 ± 0.06 mL/h/kg	1.1 ± 0.4 mL/h/kg	6.6 ± 1.8 mL/h/kg
Protein binding	About 99%	About 91%	About 98%
Active metabolites	*N*-desmethyldiazepam, oxazepam	None	α-Hydroxy-midazolam
Comment	Useful alternative to lorazepam for intravenous treatment of premonitory and early status epilepticus, serial seizures and acute symptomatic seizures. Rectal diazepam administration is becoming less commonly used, because buccal and, to a lesser extent, intranasal midazolam provide a more socially acceptable alternative	Lorazepam is the preferred agent for the intravenous treatment of premonitory and early status epilepticus, serial seizures and acute symptomatic seizures	The usefulness of intravenous midazolam is mainly as a continuous infusion in the management of refractory status. The buccal and, to a lesser extent, the intranasal routes are increasingly used for pre-hospital emergency management by non-medical personnel

Introduction

Henry Gastaut was the first to describe, in 1965, the use of intravenous (i.v.) diazepam for the treatment of status epilepticus (SE) [1]. Benzodiazepines continue to be widely used in the management of acute seizure emergencies, such as serial seizures and early and established status epilepticus [2,3].

The treatment of status epilepticus is discussed in detail in Chapter 18. This chapter will review the basic pharmacology and pharmacokinetics, as well as the therapeutic and adverse effects of i.v. diazepam, lorazepam and midazolam. Alternative routes of administration for emergency uses of these drugs are also reviewed.

Chemistry

Diazepam

Diazepam (Fig. 34.1a) corresponds to 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzo-diazepin-2-one. Its chemical formula is $C_{16}H_{13}ClN_2O$, its molecular weight is 284.8 and its pK_a is 3.4 (3.2–3.7).

Diazepam is highly lipophilic but water insoluble and has to be prepared in 40% propylene glycol and 10% ethyl alcohol (Valium®, Roche) [4] or as an emulsion (Diazemuls®, Pharmacia & Upjohn) [5]. Diazepam solution can be diluted (maximum two ampoules of 5 mg/2 mL) in not less than 250 mL of 5–10% dextrose, normal saline or Ringer's if necessary. Diazemuls® can be diluted up to a maximum concentration of 200 mg per 500 mL of solvent. A rectal tube formulation is available (cremophor EL, Stesolid®, Diastat®) [6].

Lorazepam

Lorazepam (Fig. 34.1b), or 7-chloro-5-(2-chlorphenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one, has a chemical formula of $C_{15}H_{10}Cl_2N_2O$. Its molecular weight is 321.16 and its pK_a is 1.3.

Lorazepam is only moderately lipophilic, water insoluble (0.08 mg/mL) and undissociated at physiological pH [7]. The usual preparation is a 1-mL ampoule containing 4 mg.

Midazolam

Midazolam (Fig. 34.1c) is 8-chloro-6-(2-fluorphenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine. Its chemical formula is $C_{18}H_{13}ClFN_3$, its molecular weight is 325.8 and its pK_a is 6.15. Midazolam is an imidazobenzodiazepine that readily forms a water-soluble salt. At physiological pH the ring structure closes and the drug becomes lipid soluble and crosses the blood–brain barrier [8].

Midazolam is provided in an acidic aqueous solution (pH 3.3–3.5) and can be diluted with 5% dextrose, normal saline and Ringer's lactate [9]. The parenteral aqueous solution can be administered i.v. or intramuscularly rectally, buccally, orally and nasally [9].

Mechanisms of action

Diazepam, lorazepam and midazolam have a rapid onset of clinical effect, mainly because they are highly lipophilic and therefore rapidly penetrate the blood–brain barrier [10]. However, due to this property they also redistribute relatively rapidly from the brain to other lipophilic tissues in the body, a process which is much more important than the elimination half-life in determining the duration of the antiseizure effect after bolus doses [11,12]. The duration of anticonvulsant action after single conventional i.v. doses is short for diazepam (<2 h) and midazolam (3–4 h) and longer for lorazepam (up to 72 h) [13–16].

All benzodiazepines in clinical use share a capacity to enhance the binding of γ-aminobutyric acid (GABA) to the $GABA_A$ receptor to a variable degree, and to amplify the increase in chloride channel conductance triggered by the GABA–$GABA_A$ receptor interaction. This results in neuronal hyperpolarization. Benzodiazepines do not activate $GABA_A$ receptors directly, but rather bind to a specific site at the benzodiazepine–$GABA_A$ receptor–chloride channel complex and require the presynaptic release of GABA to express their effects [17].

The amplification of $GABA_A$ responses by benzodiazepines occurs at drug concentrations less than 100 nM. At higher concentrations, corresponding to those achieved during treatment of status epilepticus, the actions of benzodiazepines may also involve other mechanisms, including inhibition of uptake of adenosine

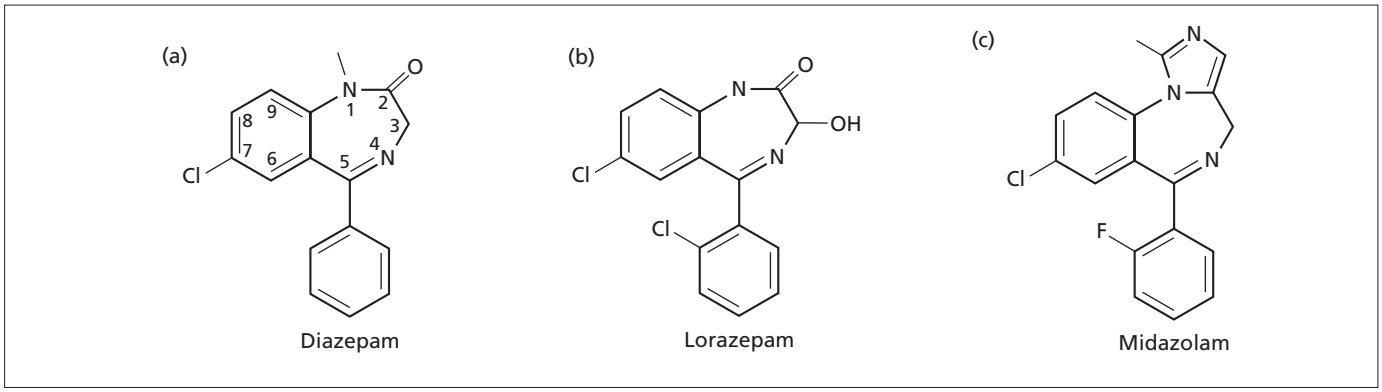

Fig. 34.1 Chemical structure of (a) diazepam, (b) lorazepam and (c) midazolam.

[18,19], as well as GABA-independent inhibition of calcium currents, calcium-dependent release of neurotransmitters and voltage-dependent block of high-frequency sodium channels [20–22].

Functional alterations of the GABA receptor during status epilepticus are reported and may be a key mechanism for treatment failures in advanced status [23–25]. Some authors therefore recommend a combination of drugs, with different mechanisms of action, early at the onset of status [26].

Pharmacokinetics

Diazepam

Absorption and distribution

After an i.v. injection of 10–20 mg diazepam at 2–5 mg/min, peak serum levels of 700–1600 μg/L are reached within 3–15 min [27,28] (Table 34.1). Serum levels sufficient to suppress seizure activity (200–600 μg/L) [29], however, are usually reached within 1 min of i.v. dosing. After intramuscular administration of a single 10- to 20-mg dose, diazepam peak serum concentrations of 35–300 μg/L are reached within 30–60 min [30,31]. The high variability and the delayed peak does not encourage use of the intramuscular route in status epilepticus.

After rectal administration of solution or gel (e.g. Stesolid® or Diastat®) diazepam is rapidly absorbed and peaks within 3 and 30 min [6,32–36]. Concentrations between 300 and 800 μg/L are reached within 4–45 min, and peak concentrations of 600–1400 μg/L within 10–60 min, after instillation of 1 mg/kg rectal tube solution. Absorption is faster in children, and effective serum levels in children are reached within 5–10 min. The bioavailability of rectal diazepam is 80–100% [33]. Variability in peak concentration and a lower bioavailability in adults may be due to patient-related factors or administration techniques. One study found unreliable bioavailability of 50% [37]. In adults with repetitive seizures, 3 of 39 rectal applications (one with 20 mg and two with 30 mg diazepam) were associated with persistent seizure activity; in two of them only subtherapeutic levels below 120 μg/L were found [36].

Distribution

After i.v. single-bolus administration diazepam distributes rapidly across the blood–brain barrier and into lipophilic tissues, and the decay of serum concentration shows distinct distribution and elimination phases, which can be described approximately by a two-compartment model. The volume of distribution ranges from 1 to 2 L/kg and is larger in women and in the elderly [38–41].

Serum diazepam levels after a single 5- to 10-mg injection fall rapidly to subtherapeutic concentrations (<200 μg/L) within 20 min. Only 3–5% of the total initial dose remains in brain tissues [38]. After repeated injections or continuous infusion, however, the decay of serum concentration is attributable not to redistribution into the peripheral compartments (fat stores), but to the much slower process of hepatic metabolism and clearance. Thus, repeated doses and continuous infusions carry a risk of sudden and unexpected potentially fatal cardiorespiratory depression.

Diazepam is highly bound (97–99%) to plasma proteins, mainly albumin and in to a lesser extent α_1-acid glycoprotein [42]. Protein binding is reduced in liver cirrhosis [43], renal failure [44–46], in neonates and in the elderly [47,48]. Cerebrospinal fluid (CSF) concentrations of diazepam and its main metabolite, *N*-desmethyldiazepam, correlate with the unbound fraction in serum [49], but concentrations of diazepam fall rapidly in the first hour after injection, a finding consistent with the relatively weak binding of diazepam to benzodiazepine receptors (which is in contrast to lorazepam).

Elimination

Diazepam is extensively metabolized by the hepatic microsomal enzymes CYP2C19 and CYP3A4 to several active metabolites, including *N*-desmethyldiazepam, temazepam and oxazepam [50,51]. The main pharmacologically active metabolite, *N*-desmethyldiazepam, has a longer half-life than diazepam and may be responsible for some of the antiepileptic effects of diazepam during prolonged use, but there is little indication for its use in the emergency treatment of status epilepticus. The elimination half-life of diazepam is between 18 and 100 h (mean 20–40 h). It is reduced by one-third in patients treated with enzyme-

Table 34.1 Diazepam pharmacokinetic parameters.

Bioavailability (%)	Fraction bound (%)	Time to peak (min) [peak concentration (μg/L)]	Volume of distribution (L/kg)	Half-life (h)	Clearance (mL/h/kg)	Primary route of elimination	Active metabolites
Oral: 100 ± 14	98.7 ± 0.2	Intravenous: 3–15 min, [700–1600] after 10–20 mg bolus at 2–5 mg/min	1.1 ± 0.3	43 ± 13	0.38 ± 0.06	Oxidative demethylation	Desmethyldiazepam, oxazepam
Rectal: 80–100	↓ elderly, neonates, hepatic failure, renal failure, hypoalbuminaemia	Rectal: 3–30 min [600–1400] after 1 mg/kg	↑ elderly, hepatic failure, hypoalbuminaemia	↑ elderly, hepatic failure	↑ hypoalbuminaemia; ↓ hepatic failure		

Reported values (mean ± SD, or range) refer to healthy adults not receiving interacting co-medications.
↑, increased; ↓, decreased.

Table 34.2 Lorazepam pharmacokinetic parameters. Reported values (mean ± SD, or range) refer to healthy adults not receiving interacting co-medications.

Bioavailability (%)	Fraction bound (%)	Time to peak (min) [peak concentration (μg/L)]	Volume of distribution (L/kg)	Half-life (h)	Clearance (mL/h/kg)	Primary elimination route	Active metabolites
Oral: 93 ± 10	91 ± 2 ↓ ⇌ elderly, hepatic failure; ⇌ renal failure, patients with burns	Intravenous: 1–5 min, [70–300] after 5 mg bolus at 2 mg/min	1.3 ± 0.2 ↑ renal failure, patients with burns; ⇌ elderly, acute renal hepatitis	14 ± 5 ↑ neonates, hepatic failure, renal failure; ⇌ elderly, acute viral hepatitis	1.1 ± 0.4 ↑ patients with burns; ⇌ elderly, hepatic failure, acute viral hepatitis	Glucuronidation	None

↑, increased; ↓, decreased; ⇌, unchanged.

inducing drugs. The half-life of the drug is about 10 h in infants and about 20 h in children. Neonates, however, may show a long half-life, particularly if born prematurely. The half-life of diazepam is prolonged in the elderly (about 60–90 h), in obese patients and in patients with hepatic failure (99–164 h) [43,52], partly as a result of an increased volume of distribution and partly due to reduced drug clearance. Diazepam is not excreted into the bile in significant amounts, and only 2–5% is excreted unchanged in the urine [53].

Lorazepam

Absorption

In an open-label trial in status epilepticus, a minimum effective serum level of 30.5 μg/L was found 15 min after a single bolus of 4 mg lorazepam (rate 2 mg/min) (Table 34.2). The average concentration was 60.1 μg/L at 15 min and 51.7 μg/L at 120 min [54]. In seven patients who were treated with 5 mg lorazepam i.v. for status epilepticus, mean plasma concentrations after 30 s, 1, 2, 4 and 10 min were 272, 237, 170, 106 and 80 μg/L. In a study in healthy subjects [55], serum levels after a single bolus injection of 5 mg lorazepam remained above 30 μg/L for 18 h [7]. In the Veterans Affairs (VA) trial in status epilepticus, serum lorazepam levels of 73–328 μg/L were found immediately after an infusion of 0.1 mg/kg at a maximum rate of 2 mg/min, and declined to 45–163 μg/L after 15 min. There was no difference in concentration between those patients whose status was stopped and those whose status was not controlled [7,15].

Lorazepam has also been administered by the rectal route, but unlike diazepam rectal absorption is erratic and unreliable [56]. Lorazepam is therefore not recommended for rectal administration.

Distribution

The distribution of lorazepam after i.v. injection is described by a two-compartment model with a distribution half-life between 1 and 30 min [57,58]. The apparent volume of distribution is approximately 1 L/kg (0.91–1.3) [7], and it is slightly decreased in the elderly, but increased in obese patients and in patients with liver cirrhosis [59,60].

Lorazepam is highly protein bound (>90%) and the unbound fraction is unchanged even at concentrations up to 10 000 μg/L [61]. Protein binding is decreased in the elderly, while gender has no effect on protein binding [62].

Lorazepam crosses the blood–brain barrier rapidly. Because its lipid solubility is lower than that of diazepam, there is little accumulation in body fat stores. The CSF concentration is 10–15% of the blood levels [40], suggesting a passive diffusion into the brain, determined by the free fraction. A 40-fold higher brain concentration compared with the serum levels was found in the brain of Sprague–Dawley rats, a finding which is consistent with its strong binding to benzodiazepine receptors in the brain [63].

Elimination

Lorazepam is cleared primarily by glucuronidation at the 3-hydroxy group [7] and it has no active metabolites [57]. The elimination half-life of lorazepam is 15 h (range, 8–25 h) in healthy individuals [57]. The half-life is similar in healthy elderly [60], but it is shorter in children (8–13 h) [64], and prolonged in neonates [65] and in patients with liver cirrhosis (approximately 50% increase) [59]. Due to the concomitant increase in volume of distribution, there is no effect on clearance in patients with liver cirrhosis [7]. There was no significant change in lorazepam clearance in patients with acute viral hepatitis [59] and patients with renal impairment compared with healthy controls [66].

Midazolam

Absorption

After parenteral administration of the acidic aqueous solution as a single bolus, midazolam becomes highly lipophilic at physiological pH. Therefore, there is a rapid onset of action with peak sedation after 3 min of i.v. dosing [8], but only a short duration of action is observed (Table 34.3). Peak concentrations following a single 5-mg i.v. bolus are 113 ± 16 μg/L [67]. After intramuscular injection, peak concentrations are reached within 20–30 min, with 91% bioavailability for midazolam hydrochloride [8], although much slower absorption rates may occur in some patients.

Because of the rapid hepatic clearance and consequent first-pass effect, oral bioavailability is reduced to approximately 50% in adults and 27% in children [68–70].

The buccal or intranasal routes, like the rectal route, avoid the hepatic first-pass effect. Unlike the rectal route, buccal and intra-

Table 34.3 Midazolam pharmacokinetic parameters. Reported values (mean ± SD, or range) refer to healthy adults not receiving interacting co-medications.

Bioavailability (%)	Fraction bound (%)	Time to peak (min) [peak concentration (μg/L)]	Volume of distribution (L/kg)	Half-life (h)	Clearance (mL/h/kg)	Primary route of elimination	Active metabolites
Oral, 44 ± 17; intramuscular, 91; intranasal, 83 ± 19; buccal, 74.5	98 ↓ elderly, renal failure; ⇌ hepatic failure	Intravenous, 1–5 min [113 ± 16] after 5 mg bolus at 4 mg/min; intramuscular, 20–30 min; intranasal: 10–15 min [72.2 ± 27.3] after 0.1 mg/kg; buccal: 15–90 min [35.6–77.9] after 5 mg	1.1 ± 0.6 ↑ obesity; ⇌ hepatic failure; ↓ neonates	1.9 ± 0.6 ↑ elderly, obesity, hepatic failure	6.6 ± 1.8 ↑ renal failure; ↓ neonates, hepatic failure; ⇌ obesity, children	Oxidation	α-Hydroxymidazolam

↑, increased; ↓, decreased; ⇌, unchanged.

nasal applications are socially acceptable and widely preferred by doctors, caregivers and patients [71]. Intranasal administration of midazolam has been extensively investigated in children [72–76] and adults [77], and is associated with a bioavailability of 78% with peak plasma concentrations of 72.2 ± 27.3 μg/L at 10 min after intranasal administration of 0.1 mg/kg [78]. However, to apply a therapeutic dose of midazolam into the nose of an adult, 2–3 mL of the solution needs to be instilled, which leads to discomfort, lacrimation and local burning [79]. A useful alternative is a concentrated form of an intranasal spray (2.5 mg in 90 μL), which was well tolerated in six healthy adults, with a bioavailability of 83% and peak concentrations of 71 ± 25 μg/L after 14 ± 5 min following administration of a 5-mg dose [80]. The buccal/sublingual route offers the advantage of good tolerability, even with larger volumes of solution [81]. In a study in eight healthy volunteers [72], buccal administration of 5 mg midazolam resulted in a peak serum concentration of 55.9 μg/L (range, 35.6–77.9 μg/L) at 30 min (range, 15–90 min) and a bioavailability of 74.5%

Distribution

After i.v. injection, midazolam is widely and rapidly distributed with a distribution half-life of 6–15 min [9]. The volume of distribution is 1–2.5 L/kg [82], and is higher in obese, elderly subjects and women [83,84]. Midazolam is highly bound to plasma proteins (94–98%) [85]. In experimental animals, the drug equilibrates between plasma and the CSF within a few minutes [12].

Elimination

Midazolam is extensively metabolized by CYP3A4 and the closely related enzyme CYP3A5 [68], and less than 1% of a dose is excreted unchanged. The main metabolite, α-hydroxymidazolam, which results from oxidation of the imidazole ring [86], is pharmacologically active but has a shorter half-life than midazolam and therefore contributes little to the overall clinical effect [87]. The hydroxylated metabolite is excreted in urine in glucuronide form [85].

The elimination half-life of midazolam is short and ranges from 1.5 to 4 h [88], but is markedly prolonged (up to 10 h) in the elderly [84,89], in neonates [90,91] and, to a lesser degree, in children [85]. The clearance of midazolam ranges from 0.24 to 0.53 L/min in healthy individuals [87,88] and is reduced in patients with hepatic disease [92], congestive heart failure [93] and probably also renal failure [9].

Drug interactions

Because enzyme-inducing antiepileptic drugs (AEDs) such as carbamazepine, phenytoin and barbiturates stimulate the activity of cytochrome P450 enzymes [88] and glucuronyltransferase [88], an increase in the clearance of diazepam, lorazepam and midazolam should be anticipated in patients co-medicated with enzyme inducers. In the case of midazolam, induction of first-pass metabolism by carbamazepine or phenytoin has been shown to cause a dramatic reduction in oral bioavailability [88], but a smaller degree of interaction is expected when midazolam is administered by the i.v., intramuscular, buccal and intranasal routes, which avoid the hepatic first-pass effect.

Other interactions relate to inhibition of drug metabolism [88]. For example, midazolam clearance is decreased by drugs that inhibit CYP3A4, such as erythromycin, clarithromycin, ketoconazole, diltiazem, verapamil or cimetidine. Diazepam clearance has been found to be decreased by inhibitors of CYP3A4 (e.g. cimetidine, itraconazole, erythromycin) and by inhibitors of CYP2C19 (e.g. omeprazole and fluvoxamine). Lorazepam clearance is decreased by about 40% by co-administration of valproate [9]. The latter interaction was considered to have contributed to development of encephalopathy in a patient treated with a combination of these drugs [9], even though a pharmacodynamic interaction may have played a role in the clinical presentation.

Overall, the interactions described above are unlikely to have major clinical significance when benzodiazepines are used in single doses in emergency settings. They may, however, affect dose requirements in patients who need prolonged infusions for the management of refractory status epilepticus. More important interactions are likely to occur at pharmacodynamic level, and they consist in reciprocal potentiation of central nervous system (CNS) effects when benzodiazepines are co-administered with other CNS depressants.

Serum level monitoring

The use of benzodiazepines in an emergency setting is guided by direct evaluation of clinical response, and monitoring serum drug levels is of little or no value in this context.

Efficacy

Diazepam

Intravenous diazepam is still one of the most widely used drugs for the treatment of premonitory and early status epilepticus as well as serial seizures and ongoing acute seizures [2]. Its efficacy is supported by many clinical studies. Unfortunately, most of them were uncontrolled and not randomized. In addition, the definitions used for status epilepticus varied over time (30 min [94], 10 min [15], 5 min [95]), the populations studied were heterogeneous, sometimes with only a small fraction of patients meeting the criteria for generalized convulsive status epilepticus [1] and the primary endpoints differed substantially among the studies.

The non-randomized trials of diazepam in status epilepticus were reviewed by Browne and Penry in 1973 [96], Schmidt in 1985 [97] and Treiman in 1989 [98]. Overall, 20 non-randomized open-label trials (n = 531) of i.v. diazepam have been reviewed by Treiman. In these studies, diazepam provided lasting control of seizures in 39–100% of patients [1,34,99–116]. Further, five non-randomized studies not included in the above review [13,117–120] reported similar success rates of between 65% and 100%. However, in many of the patients (in some studies more than 50%) [110,113,118,120] who were treated with diazepam, seizures recurred shortly after initial cessation of seizure activity. The reason for a high recurrence rate is due to a fast initial fall in serum drug levels [37]. The formerly common use of a continuous infusion of diazepam after initial success [16,111] to prevent the rapid fall in serum drug levels has now fallen from favour, due to the danger of drug accumulation and redistribution with resulting severe cardiorespiratory depression.

Apart from the VA randomized trial [14] (which compared diazepam followed by phenytoin with i.v. lorazepam and with other treatments and is discussed below in the section on lorazepam), three randomized controlled trials with 289 participants compared the effect of i.v. diazepam with i.v. lorazepam [14,121,122]. The results of these studies were evaluated in three different meta-analyses [123–125]. One study in a pre-hospital setting used lower than usual initial benzodiazepine dosages (5 mg diazepam or 2 mg lorazepam) [14]. Another study included children only [122]. When the data from the randomized trials were analysed together, there was no difference in mortality between the groups. However, lorazepam was superior to diazepam in stopping status epilepticus [32/130 versus 51/134 participants, relative risk (RR) 0.64, 95% confidence interval (CI) 0.45–0.90) and with lorazepam fewer patients required a different drug or general anaesthesia (32/130 versus 52/134 participants; RR 0.63, 95% CI 0.45–0.88) (data derived from ref. 124).

Non-randomized trials using rectal diazepam for the treatment of seizure clusters, prolonged seizures and early status epilepticus have reported termination of seizures in approximately 80% within 15 min [126–128]. Two randomized placebo-controlled trials using rectal diazepam in acute repetitive seizures were performed in adults and children [129–131]. In both studies, rectal diazepam reduced the risk of ongoing seizures compared with placebo (RR 0.43, 95% CI 0.30, 0.62), with a non-significant trend towards more adverse events in the diazepam group (RR 1.50, 95% CI 0.94–2.37) [123]. One randomized study compared the efficacy of 30 mg diazepam with 20 mg diazepam rectally in adults with serial seizures [36]. A 30-mg rectal diazepam dose reduced the risk of ongoing seizures significantly (RR 0.39; 95% CI 0.18–0.86, compared with 20 mg), without difference in adverse event rate (RR 0.90; 95% CI 0.53–1.53) [36,123]. Rectal diazepam was used as active comparator in six randomized trials with intranasal midazolam [132,133] and buccal midazolam [134–137] with similar efficacy (see section below on midazolam). Evidence concerning the use of rectal (and oral) diazepam as intermittent prophylaxis against recurrent febrile seizures is discussed in Chapter 14.

Lorazepam

Lorazepam is an extremely potent anticonvulsant. Its binding characteristics to the benzodiazepine receptor are quite similar to those of clonazepam [138], but the longer duration (up to 72 h) of the clinical effect of lorazepam suggest that other mechanisms may be involved in its action. The longer duration of action of lorazepam is a very important advantage over diazepam because, when used intravenously in an outpatient setting (as commonly done in Finland, Germany, Austria and many other countries), it provides time to transport the patient safely to the nearest hospital. Additional important advantages are that the risk of seizures relapsing is reduced, and that physicians are given ample time to establish diagnosis and to determine the optimal longer-term treatment.

There has been some concern that the onset of the anticonvulsant effect of lorazepam might be slow, because of lower lipid solubility of the drug compared with diazepam [55,139]. However, this concern is not supported by results of clinical studies, which showed a rapid onset of 3 min (range 1–15 min) in neonates [140], children [141–143] and adults [54,121]. Similarly, early effects on the EEG are noticed after 30 s in healthy volunteers [144]. These results have led to general acceptance of lorazepam as first-line treatment of premonitory and early status epilepticus [2,3,145,146], an indication supported by numerous non-randomized and by five randomized controlled trials [14,15,121,122,147].

More than 483 patients were included in non-randomized trials between 1975 and 2002, with overall success rates between 63% and 100% [13,54,119,140–143,148–159]. These studies vary considerably in their design, definitions of status epilepticus, treatment protocols and types of status. Only a small proportion of patients had generalized convulsive status and most patients included in uncontrolled studies had previous epilepsy.

Five randomized studies have compared lorazepam with diazepam [14,121,122], with midazolam [147] and with phenytoin, diazepam plus phenytoin, and phenobarbital [15]. Three of these studies were double-blinded [14,15,121], one is published only in abstract form [147] and two included children [122,147]. Three meta-analyses are available [123–125]. Analysis of the data led to the conclusion that, compared with diazepam, patients treated

with lorazepam in the early phase of status epilepticus had a lower risk for seizure continuation [32/130 (25%) versus 51/134 (38%) participants; RR 0.64; 95% CI 0.45–0.90], and a lower risk of continuation of status epilepticus leading to treatment with another drug or general anaesthesia [32/130 (25%) versus 52/134 (39%) participants; RR 0.63, 95% CI 0.45, 0.88] [124]. There was no significant difference for respiratory failure/depression, hypotension and deaths between the groups [123,124]. In the VA study, lorazepam controlled 67% of all patients with overt status epilepticus and was superior to phenytoin alone (51%), although there was no statistical significant difference with respect to diazepam plus phenytoin (59.6%) or phenobarbital (63%) [15].

Midazolam

Midazolam was introduced in the early 1980s as a short-acting sedative for minor operative procedures. Kaneko reported the first case of successfully treated status epilepticus with i.v. midazolam in 1983 [160]. Soon after that, midazolam became widely used in early status epilepticus despite its obvious short duration of action and high risk of recurrence of seizure activity. In refractory status epilepticus, midazolam is used as a continuous infusion, to overcome its short-lasting clinical effect. Due to its water solubility, which is unique among the clinically used benzodiazepines, alternative routes of administration (intramuscular, intranasal, buccal/sublingual) are feasible and offer a singular advantage over other benzodiazepines.

The efficacy of i.v. midazolam in acute seizure emergencies has been demonstrated in 22 non-randomized [120,161–181] and one randomized trial [182], including more than 900 patients.

In the past years, 10 non-randomized [183–193] and seven randomized controlled trials using intranasal [132,133,194], buccal [134,136,137] and intramuscular [195] midazolam have been performed. Most studies included children, and some were performed in neonates [178,180]. Buccal, nasal and intramuscular midazolam were mainly assessed for the treatment of acute repetitive seizures and early status epilepticus, whereas most studies using i.v. midazolam as continuous infusion included patients with refractory status. Overall, more than 2000 patients treated with midazolam in various forms for acute seizures or status epilepticus have been reported.

Studies with i.v. midazolam

After the first case report [160], small case series using i.v. midazolam in the treatment of early status epilepticus found excellent response rates, up to 100% [177], but, as expected, the short duration of action led to a disappointingly high number of relapses (75%) within a short time. In a study from a large centre in Serbia, five of seven patients with early status epilepticus experienced severe respiratory depression and hypoventilation after 15 mg midazolam i.v. at a rate of 5 mg/min [120]. In children, initial doses for early status and acute seizures of between 0.1 and 0.3 mg/kg have been used, followed by continuous infusion, most often started at 0.06 mg/kg/h and increasing stepwise up to 0.48 mg/kg/h until complete suppression of seizure activity [161, 164,166,167,170,172] with excellent overall response rates between 64.5% and 98.5%. In one study, exceptionally high continuous infusion rates up to 1 mg/kg/h have been reported [164]. In children, there have been virtually no reports of local reactions or systemic adverse events in these case series, except for one study which found a 3% rate of respiratory depression requiring ventilatory support [167]. In refractory childhood status, similar doses have been used, with response rates between 76% and 100% and uniformly low adverse event rates [163,165,174,175]. Inclusion criteria in the paediatric studies varied considerably and probably not all patients qualified for the definition of status epilepticus.

In adults with refractory status epilepticus, i.v. midazolam has been given as a continuous infusion [162,168,169,173,176,179,196]. Claassen *et al*. reviewed 193 patients with refractory status epilepticus treated with i.v. midazolam (n = 54), propofol (n = 33) or pentobarbital (n = 106) and found an overall initial response rate of 80%, which was less than that found with pentobarbital (92%) [197]. Patients treated with i.v. midazolam (loading dose 0.2 mg/kg, infusion rate ranging from 0.08 ± 0.04 mg/kg/h to 0.23 ± 0.17 mg/kg/h) experienced breakthrough seizures more often (51%) than those treated with propofol (15%) and pentobarbital (12%). Withdrawal seizures were also more common with midazolam than with propofol and pentobarbital (63% versus 46% versus 43%, respectively). However, patients given i.v. midazolam experienced significantly fewer episodes of hypotension requiring pressor agents (30% versus 42% versus 77%, respectively). The authors concluded that none of these drugs is superior to the others, and that the lower response rate with midazolam is compensated by better tolerability. Naritoku and Sinha found an unexpectedly slow clearance after prolonged i.v. midazolam infusion, with terminal half-lives of 52.1 and 20.1 h, and suspected time-dependent pharmacokinetic changes after prolonged midazolam use [181]. This could contribute to a more prolonged awakening after long-term treatment of refractory status epilepticus.

One open-label randomized trial has been conducted in 40 children aged 2–12 years with refractory status (motor seizures uncontrolled after two doses of diazepam 0.3 mg/kg and a 20 mg/kg phenytoin infusion) [182]. Patients were randomized to continuous i.v. midazolam or i.v. diazepam with incremental dosages. Status was controlled in 86% of children with midazolam and 89% with diazepam, but relapse rates were significantly higher in the midazolam group (57% versus 16%). About half the patients needed mechanical ventilation and 40% had hypotension.

Studies with alternative routes of administration

Early reports using intramuscular midazolam [190–192,198,199] found good tolerability and response rates between 80% and 92%. In two studies [188,195], one of which was randomized [195], intramuscular midazolam was compared with i.v. diazepam in early status epilepticus in children. Though response rates did not differ significantly, patients in the midazolam group received their medication earlier (3.3 ± 2.0 versus 7.8 ± 3.2 min), and time to cessation of seizures was shorter (7.8 ± 4.1 versus 11.2 ± 3.6 min) [195].

Intranasal application is easy and may be advantageous in the early phase of status or in the treatment of prolonged or serial seizures in childhood. Three randomized controlled trials compared intranasal midazolam 0.2 mg/kg with i.v. diazepam 0.3 mg/kg [194] or rectal diazepam 0.3 mg/kg [133,193] in acute seizures [132,133] and prolonged febrile convulsions (>10 min) [194]. The initial response rate was uniformly excellent, between 82% and

100%, and midazolam was not inferior to the comparator. In one study, intranasal midazolam was even superior to rectal diazepam (87% versus 60%) [132]. Patients given intranasal midazolam received their treatment significantly earlier and their seizures ceased sooner than with rectal or i.v. diazepam [133,194].

Four randomized controlled trials, including 564 patients, compared the efficacy of buccal midazolam with rectal diazepam in early childhood status epilepticus [134–137]. Three studies found no difference in efficacy (buccal midazolam versus rectal diazepam: 75% versus 59% [134], 57% versus 67% [136] and 78% versus 85% [137]). However, all authors concluded that the buccal route was easier to use and socially more acceptable for initial treatment of early status in childhood. In addition, one study found buccal midazolam even more effective than rectal diazepam (56% versus 27%) [135]. Thus, buccal midazolam is now a widely accepted and effective treatment for acute seizures in childhood.

Adverse effects

Diazepam

Systemic adverse effects and CNS toxicity

Respiratory depression, hypotension and sedation are the main risks of all intravenously used benzodiazepines. After i.v. administration of diazepam for status epilepticus and other indications, mild to severe hypotension or respiratory depression occurred in 5.2% of 246 patients, including one fatal case (0.4%), reviewed by Schmidt [200]. Browne and Penry reviewed the reports on 439 patients in 35 articles and found 16 cases of respiratory depression and 10 cases of hypotension in nine reports [101,109,113,114,201–203]. In three reports, previous treatment with barbiturates was regarded as a predisposing factor for diazepam-induced respiratory depression [101,113,114]. In the randomized trials using i.v. diazepam, 7% (7/100) of the patients had hypotension [14,122] and 10% (15/153) had respiratory depression/failure [14,121,122]. When combined with subsequent i.v. phenytoin, 20% (22/113) of patients had respiratory depression/failure and 29% (33/113) had hypotension [15,204]. A meta-analysis of three randomized controlled studies comparing i.v. diazepam versus lorazepam in the treatment of status epilepticus [14,121,122] found no difference in risk of respiratory failure/depression (RR 0.78, 95% CI 0.35–1.74) or hypotension between the drugs [124]. A prospective study analysed 122 episodes treated with either i.v. or rectal diazepam in 97 children, and found an overall incidence of respiratory depression of 9%. Of the patients with respiratory depression, 72% needed ventilatory support after diazepam administration [205].

Several risk factors for respiratory depression and hypotension have been described in open studies or case reports, including previous use of barbiturates, chlordiazepoxide, methaqualone, gallamine or lidocaine [101,113,206–208], older age [209,210] and liver disease [211]. Patients with respiratory disorders and muscular disease are also likely to be at greater risk, at least for respiratory depression. Although not formally assessed, the rate at which the bolus is injected seems to be particularly crucial for the development of respiratory depression and hypotension [212,213]. A rate of 2–5 mg/min should not be exceeded [2].

In contrast to Diazemuls®, the Valium® preparation contains propylene glycol as a solvent, which may also lead to systemic effects. A syndrome of propylene toxicity with otherwise unexplained anion gap, metabolic acidosis, hyperosmolality, seizures, cardiac arrhythmias and clinical deterioration has been described [214,215]. Because the use of continuous diazepam infusion is strongly discouraged [2], this syndrome is probably very uncommon.

Local tissue irritation

Local pain, phlebitis and venous thrombosis may occur after i.v. diazepam [216,217]. A retrospective study found thrombophlebitis in only 3.5% of more that 1500 i.v. injections during gastrointestinal procedures [218,219]. A retrospective survey of 15 813 injections found no significant local vascular complications. However, severe local reactions have also been reported [220,221]. Local reactions are associated with polypropylene glycol-based preparations and are not reported with diazepam fat emulsions (Diazemuls®) [222]. The best prevention measures against local vein reactions include administration in an antecubital vein [223], flushing with saline [224] and injection rates below 5 mg/min.

The rectal solution or gel is generally well tolerated. Some patients report a burning sensation in the rectum [129,225], but there is no evidence for mucosal damage.

Paradoxical effects

Induction of tonic status epilepticus in patients with Lennox–Gastaut syndrome has been described after use of i.v. diazepam [226–228]. Seizure aggravation or induction of acute symptomatic status epilepticus by diazepam in epilepsy syndromes other than Lennox–Gastaut syndrome has not been observed.

Lorazepam

Systemic adverse effects and CNS toxicity

The most common adverse effects of lorazepam, as with other benzodiazepines, involve the CNS. Drowsiness is common and should be expected in all patients after i.v. injection. However, severe stupor or coma is rare, even after extremely high doses with serum drug levels of 300–600 μg/L [229,230]. Respiratory depression with hypoventilation was found in 10.3% of adult patients treated with lorazepam in the VA study [15]. In a study in children, only 3% had signs of respiratory depression [122]. Interestingly, respiratory depression seems to occur after the first injection, if at all, but not after repeated use [7,143]. It has been claimed that co-medication is not a major risk factor for respiratory depression/failure [231], based on studies analysing the influence of morphine and meperidine as co-medication [232,233]. However, this view was not supported by the results of a prospective randomized double-blind study in patients scheduled for coronary artery bypass graft [234]. Other co-medications were not studied, and pharmacodynamic interactions may have to be anticipated in patients concurrently treated with other CNS depressants. Patients with respiratory disorders and muscular disease are also likely to be at greater risk of respiratory depression. Drug-induced hypotension was rare in one of the double-

blind randomized trials [121], but was observed in 26% of patients who received lorazepam in the VA study [15].

Local tissue irritation

Local pain and irritation may occur, but they are less frequently reported than with diazepam [235]. Dilution of lorazepam in 20 mL of 5% dextrose or Ringer's lactate diminishes the risk of pain, local irritation and thrombophlebitis [230,236].

Paradoxical effects

Similarly to diazepam, there are few reported cases of tonic status epilepticus in patients with Lennox–Gastaut syndrome after i.v. use of lorazepam [142,153,228]. No other paradoxical effects of lorazepam have been reported.

Midazolam

Systemic adverse effects and CNS toxicity

Respiratory depression and hypoventilation are dose-related phenomena and were reported more frequently in early case series [120] and in anaesthetic studies [237], which use higher doses. Patients with respiratory disorders and muscular disease are likely to be at greater risk of respiratory depression. In childhood refractory status epilepticus treated with a continuous midazolam infusion, hypotension may occur in up to 40%, and respiratory depression requiring mechanical ventilation in up to 50% [182]. In view of the prolonged half-life and reduced clearance, systemic toxicity is more likely to occur in elderly patients. However, tolerability is good, particularly when the intramuscular, intranasal or buccal routes of administration are used in the early phase of status epilepticus.

Local tissue irritation

Due to the solubility of midazolam in water, the solution is virtually devoid of risk of causing local venous irritation or thrombophlebitis [216]. In a prospective study, venous complications were observed in 22 of 62 patients receiving i.v. diazepam for sedation, compared with 1 of 60 patients given i.v. midazolam [238].

Paradoxical effects

Seizure aggravation or induction of tonic seizures have not been observed with midazolam.

Place in current therapy

Because of its high efficacy and long-lasting effect, lorazepam is usually the preferred choice for the first-line i.v. management of premonitory and early status epilepticus, serial seizures and acute symptomatic seizures. Its efficacy in generalized convulsive status epilepticus has been demonstrated in randomized controlled trials. Its advantages and disadvantages are summarized in Table 34.4.

Midazolam, administered by the buccal route, is a widely used first-choice agent for emergency management of acute seizure disorders by non-medical personnel, prior to admission to hospital. The intranasal route may also be used for this indication, particularly in children, but its value compared with the buccal route is less established (Table 34.5). The main limitation of midazolam when given by bolus injection or by the buccal or intranasal route is its short duration of action, which may result in re-emergence of seizure activity. In a hospital setting, midazolam's main value is in providing a treatment option, as a continu-

Table 34.4 Indications, dosing information and advantages versus disadvantages of lorazepam in the emergency treatment of seizure disorders.

Indications	*Adults and children:* premonitory and early status epilepticus (preferred drug in stage 1 of status epilepticus), serial seizures, acute symptomatic seizures
Usual dosages	*Intravenous bolus (undiluted):* 4–8 mg (adults), 0.1 mg/kg (children), usual injection rate 2 mg/min (adults and children) strictly intravenously *Intramuscular, intranasal, rectal:* not recommended *Continuous intravenous infusion:* not recommended
Advantages	Rapid onset of action by the intravenous route Long-lasting effect (>24 h) after a single injection Proven efficacy in randomized controlled trials in generalized tonic–clonic status epilepticus Long-standing clinical experience in adults and children Extensively studied pharmacology and pharmacokinetics Little risk of accumulation
Disadvantages	Sedation, respiratory depression, hypotension Polypropylene solvent in the solution may cause reactions at the injection site and systemic adverse effects with prolonged use

Table 34.5 Indications, dosing information and advantages versus disadvantages of midazolam in the emergency treatment of seizure disorders.

Indications	*Adults and children* *Continuous intravenous infusion:* refractory status epilepticus *Buccal or intranasal route:* premonitory and early status epilepticus, serial seizures, acute symptomatic seizures
Usual dosages	*Intravenous:* 0.1–0.3 mg/kg bolus at 4 mg/min (children and adults) followed by infusion of 0.05–0.4 mg/kg/h (adults). Paediatric initial infusion rates are 0.03 mg/kg/h in newborns of gestational age <32 weeks; 0.06 mg/kg/h in newborns of gestational age <32 weeks and in infants <6 months; and 0.05–0.12 mg/kg/h in children >6 months. These rates may be increased according to response (see text) Higher infusion rates have been used (and may be required), both in adults and in paediatric patients *Intranasal or buccal:* 5–10 mg (adults); 0.15–0.3 mg/kg (children) *Rectal:* not recommended
Advantages	Water solubility permits alternative routes in the emergency treatment of seizures Rapid onset of action with all routes of administration Buccal and intranasal administration have proven efficacy in randomized controlled trials in children with acute seizures Intranasal and buccal routes easy and socially well accepted Lack of reactions at the infusion site Little risk of accumulation
Disadvantages	Short duration of action with risk of seizure relapse Sedation, respiratory depression, hypotension

Table 34.6 Indications, dosing information and advantages versus disadvantages of diazepam in the emergency treatment of seizure disorders.

Indications	*Adults and children:* premonitory and early status epilepticus, serial seizures, acute symptomatic seizures
Usual dosages	*Intravenous bolus (undiluted)*: 10–20 mg (adults), 0.2–0.3 mg/kg (children), injection rate 2–5 mg/min (adults and children) strictly intravenously *Rectal:* 20–30 mg (adults); 0.5–0.75 mg/kg (children) *Continuous intravenous infusion:* not recommended
Advantages	Rapid onset of action by the intravenous route Rectal formulation available Long-standing clinical experience in adults and children Extensively studied pharmacology and pharmacokinetics Widespread availability
Disadvantages	Short duration of action, due to rapid redistribution Sedation, respiratory depression, hypotension Accumulation after repeated doses and infusion, with increased risk of prolonged sedation and respiratory depression Polypropylene solvent in the intravenous solution may cause reactions at the injection site and systemic adverse effects with prolonged use

ous i.v. infusion, for the management of refractory status epilepticus.

Diazepam is more widely available throughout the world than either lorazepam or midazolam. Whenever lorazepam is unavailable, diazepam provides a very valuable alternative as an i.v. injection to treat premonitory and early status epilepticus, serial seizures and acute symptomatic seizures (Table 34.6). Its main disadvantage is the shorter duration of action compared with lorazepam due to rapid redistribution, and its risk of accumulation and redistribution after repeated doses. Rectal diazepam administration is a valuable option to treat emergency seizure situations when the i.v. route is not feasible, for example in a number of pre-hospital settings, particularly in the absence of skilled health-care personnel. However, there is a trend for rectal diazepam to be replaced by buccal or intranasal midazolam, which is more favourably socially accepted.

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35 Brivaracetam

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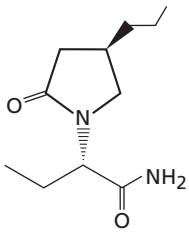

Primary indication	Adjunctive therapy of partial seizures (potential additional indications are under assessment)
Usual preparation	Tablets: 2.5, 10, 25, 50 mg Oral solution: 1, 10 mg/mL Intravenous formulation: 10 mg/mL
Usual dosage	5–100 mg/day (tentative dose range)
Dosing frequency	Twice daily
Significant drug interactions	Enzyme-inducing antiepileptic drugs and rifampicin decrease plasma brivaracetam levels. Brivaracetam may increase the plasma levels of phenytoin and carbamazepine-10,11-epoxide
Serum level monitoring	Not routinely done
Target range	Not applicable
Common/important adverse effects	Headache, somnolence, fatigue, nausea and dizziness
Main advantages	High responder rates and excellent tolerability
Main disadvantages	Limited clinical experience. Efficacy spectrum in different seizure types not yet defined
Mechanism of action	Binds to synaptic vesicle 2A (SV2A) protein. Weak blocker of voltage-gated sodium channels
Oral bioavailability	Almost complete
Time to peak levels	1–3 h
Elimination	Cleared primarily by metabolism (<10% excreted unchanged in urine) through hydrolysis of the acetamide group and secondarily through hydroxylation mediated by CYP2C9, CYP2C19, CYP3A4 and, to a negligible extent, CYP2B6 and CYP2C8
Volume of distribution	0.5 L/kg
Elimination half-life	6–11 h
Plasma clearance	0.7–1.3 mL/min/kg (values in the upper portion of the range are observed in patients co-medicated with enzyme-inducing antiepileptic drugs)
Protein binding	≤20%
Active metabolites	None known
Comment	Potentially a useful antiepileptic drug, but more data are needed to establish its optimal dose range and its place in current therapy

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Introduction

The discovery that the synaptic vesicle protein 2A (SV2A) is the principal site involved in the antiepileptic effect of levetiracetam (Keppra®) [1] stimulated UCB to search for analogues with higher affinity for SV2A than levetiracetam. Brivaracetam (ucb 34714) was identified after a primary *in vitro* screening of over 10 000 compounds, a secondary screening of 900 compounds in the mouse audiogenic seizure model, and a tertiary screening of 30 drug candidates in various other epilepsy models [2].

Brivaracetam is a novel pyrrolidone derivative with 10-fold higher binding affinity for SV2A than levetiracetam [2]. In contrast to levetiracetam, brivaracetam also displays an ability to inhibit voltage-dependent sodium channels [3]. Results of studies in animal models of epilepsy and seizures indicate that the compound has higher potency than levetiracetam, and a potential for superior efficacy in a broad range of seizure types [4]. Efficacy and tolerability results from phase IIb adjunctive therapy studies in patients with uncontrolled partial-onset seizures have been promising [5,6]. Brivaracetam is, at the time of writing, in phase III development.

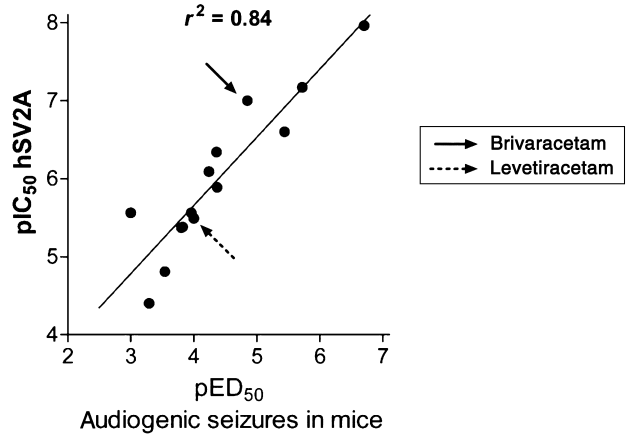

Fig. 35.1 Correlation between binding affinity to human synaptic vesicle protein 2A (hSV2A) and antiseizure potency of racetam compounds. Binding affinity (pIC_{50}) was measured in transiently transfected COS-7 cells, and antiseizure potencies [shown as the –log ED_{50}s (pED_{50}s)] were measured in the mouse audiogenic seizure model. There is a good correlation between antiseizure potency in audiogenic mice and affinity to hSV2A. Reproduced from ref. 1 with permission [© (2004) National Academy of Sciences, USA].

Chemistry

Brivaracetam {[2*S*]-2-[(4*R*)-2-oxo-4-propylpyrrolidinyl] butanamide} is a 2-pyrrolidone derivative, freely soluble in water, with a molecular weight of 212 [2].

Pharmacology

Mechanisms of action and activity in experimental models

Mechanisms of action

Preclinical studies have shown that brivaracetam binds to SV2A, with a 10-fold higher affinity than levetiracetam [2]. SV2A has been implicated in the modulation of synaptic vesicle exocytosis and neurotransmitter release [7,8] and binding to this protein is considered to be the primary mechanism for brivaracetam's anticonvulsant activity [1,2,9,10]. Indeed, there is a strong correlation between ligand affinity for SV2A and anticonvulsant potency in animal models of both partial and generalized epilepsy (Fig. 35.1) [1,10].

Additional mechanisms may contribute to the anticonvulsant activity of brivaracetam. In particular, the compound has been found to possess some inhibitory activity at neuronal voltage-dependent sodium channels, on which levetiracetam is inactive (Table 35.1) [3], and to reverse the inhibitory effects of a number of negative allosteric modulators, such as zinc and β-carbolines, on γ-aminobutyric acid (GABA)- and glycine-gated currents [12].

Table 35.1 Comparisons of the mechanisms of action of brivaracetam and levetiracetam.

	Brivaracetam	Levetiracetam
SV2A (pK_i)	7.1	6.1
Reversal of inhibition by zinc on GABA-gated currents (20 μmol) in hippocampal neurones	Reversal (1–100 μmol)	Reversal (30–1000 μmol)
Reversal of inhibition by zinc on glycine-gated currents (100 μmol) in spinal cord neurones	Reversal (3–100 μmol)	Reversal (0.1–100 μmol)
Inhibition of high voltage-activated calcium channel currents (IC_{50} value)	Inactive up to 1 mmol/L	13.9 μmol
Inhibition of voltage-gated sodium channel currents (IC_{50} value)	7 μmol	Inactive up to 1 mmol/L

From refs 1, 3, 9, 11, 12, 32–35 and 38.
GABA, γ-aminobutyric acid; IC_{50}, inhibitory half-maximal concentration; pK_i, –log of the unlabelled drug equilibrium constant.

Activity in experimental models of seizure and epilepsy

In two *in vitro* models of epileptic activity in rat hippocampal slices, brivaracetam (1–10 μmol/L) inhibited epileptiform responses induced by a high potassium/low calcium ions perfusion fluid or by addition of 5 μmol/L bicuculline methiodide (BMI) to the normal perfusion liquid. Brivaracetam showed higher efficacy and potency than levetiracetam in these models [4]. In particular, brivaracetam (3.2 μmol/L) reduced the occurrence of spontaneous bursts, while levetiracetam (32 μmol/L) was inactive against spontaneous bursts. BMI-induced increase in population spike amplitude was inhibited by brivaracetam even at 0.1 μmol/L, with the greatest effect observed at 3.2 μmol/L.

Brivaracetam shows potent activity in many *in vivo* models of seizures and epilepsy (Table 35.2) [4]. Unlike levetiracetam, brivaracetam is effective in inhibiting seizures induced in the classical

Table 35.2 Brivaracetam provides better seizure protection than levetiracetam in animal models of seizures and epilepsy.

	Brivaracetam	Levetiracetam
Acute seizure tests in normal animals		
Maximal electroshock seizures in mice		
ED_{50}, mg/kg i.p.	113	>540
Pentylenetetrazol seizures in mice		
ED_{50}, mg/kg i.p.	30	>540
Fully kindled animals		
Corneally kindled mice		
ED_{50}, mg/kg, i.p.	1.2	7.3
Hippocampal-kindled rats		
MAD, mg/kg, p.o.	0.2	54
Amygdala-kindled rats		
Motor seizure severity, MAD, mg/kg i.p.	21.2	170
Reduction of afterdischarge duration at highest tested dose (percentage)	69	13
Genetic models of chronic epilepsy		
Audiogenic susceptible mice		
ED_{50}, mg/kg, i.p.	2.4	30
Genetic Absence Epilepsy Rat from Strasbourg, MAD, mg/kg, i.p.	6.8	5.4
Seizure suppression at highest tested dose	Complete	Partial

From refs 4 and 36–38.
ED_{50}, dose which effectively protects 50% of the animals against the convulsive endpoint; i.p., intraperitoneal; MAD, minimal active dose providing significant protection against the seizure endpoint; p.o., per os (oral).

maximal electroshock and pentylenetetrazole seizure tests, albeit at relatively high doses. Audiogenic seizure-susceptible mice were better protected against clonic convulsions induced by acoustic stimuli when treated with brivaracetam than with levetiracetam [ED_{50} values = 2.4 versus 30 mg/kg, intraperitoneally (i.p.)]. In corneally kindled mice (3 mA, 3 s, twice daily), brivaracetam provided more potent protection than levetiracetam against secondarily generalized motor seizures (ED_{50} = 1.2 versus 7.3 mg/kg, i.p.). In the corneal kindling development model, pretreatment of mice twice daily with brivaracetam (0.21–6.8 mg/kg, i.p.) prior to corneal stimulation (3 mA, 3 s, twice daily) also resulted in a more potent and persistent inhibition of kindling development than observed with levetiracetam.

In hippocampal-kindled rats, a model of localization-related epilepsy, brivaracetam provided more potent protection against seizures than levetiracetam (minimal active dose = 0.21 versus 54 mg/kg, oral) [4]. In fully amygdala-kindled rats (50 Hz, 1 s, 500 μA monophasic square-wave pulses, once daily, 5 days per week), brivaracetam induced a nearly complete suppression of both motor seizure severity and after-discharge duration.

Brivaracetam significantly suppressed spontaneous spike-and-wave discharges in the Genetic Absence Epilepsy Rat from Strasbourg (GAERS), a model predictive of activity against absence epilepsy [4].

Brivaracetam also possesses more potent antiseizure and antimyoclonic activity than levetiracetam in a model of cardiac arrest-induced posthypoxic myoclonus in rats [13]. Potent anticonvulsant activity was also demonstrated in a rat model of acute, partially drug-resistant, self-sustaining status epilepticus induced by perforant path stimulation [14]. In this model, treatment with brivaracetam (20 mg/kg) shortened the cumulative duration of active seizures to 11% of the duration of controls. In comparison, 200 mg/kg levetiracetam and 10 mg/kg diazepam reduced seizure duration to 35% and 15% of control values, respectively. Brivaracetam was also shown to potentiate the effects of diazepam in this model: low doses of brivaracetam (1 mg/kg) or diazepam (1 mg/kg) alone had little effect but, when combined, they reduced the duration of active seizures to 3% of controls.

Overall, the activity profile of brivaracetam in these models is suggestive of broad-spectrum efficacy against partial and generalized seizure types.

Evidence of activity in non-epilepsy indications

Brivaracetam (2.1–68 mg/kg, i.p.) has been compared with gabapentin (30 or 60 mg/kg) in the mononeuropathic (chronic constriction injury) model and in the streptozotocin-induced diabetic model of neuropathic pain [15,16]. In both models, brivaracetam showed significant activity, increasing vocalization thresholds and displaying dose-dependent antihyperalgesia.

Brivaracetam has also been investigated in animal models of essential tremor [17]. At non-sedative doses (up to 120 mg/kg, i.p.), the compound reduced the elicited tremor index by up to 66%.

Toxicology data

In studies conducted in mice, rats and dogs, brivaracetam demonstrated low acute oral toxicity [18]. Transient dose-related central nervous system (CNS) effects were observed, generally at oral doses of 100 mg/kg and above. Brivaracetam also resulted in a slight respiratory stimulant effect above 100 mg/kg, and at 300 mg/kg it delayed stomach emptying and reduced gastrointestinal transit. No significant effects were noted on the cardiovascular system. The maximum non-lethal oral single dose in rats was above 1000 mg/kg and a no-effect level of 500 mg/kg was established based on clinical signs.

Repeated-dose oral administration of brivaracetam in animals has indicated the liver as the target organ. The non-observed adverse effect level (NOAEL) following 26 weeks of repeated administration was 15 mg/kg/day in dogs and 450 mg/kg/day in rats. In monkeys, after 39 weeks of repeated administration, the NOAEL was 900 mg/kg/day. Thus, for a dose of 100 mg/day in adult humans, the dog, the rat and monkey long-term toxicity studies provide margins of safety for hepatotoxicity of 1.2-fold in dogs, compared with 9- to 16-fold in rats and 81-fold in the monkeys.

Genotoxicity studies showed no evidence of mutagenicity or clastogenicity [18]. No adverse effects on fertility and early embryonic development were detected up to the highest tested oral dose of 400 mg/kg/day (safety margins of 18- and 30-fold in males and females, respectively). Brivaracetam has demonstrated no teratogenic potential in either the rat or the rabbit (safety margins of 57- and 14-fold in rat and rabbit fetuses, respectively). Neonatal development was also unaffected up to a dose of 300 mg/kg/day (safety margin of 13-fold in rat pups).

Pharmacokinetics

Following oral administration to healthy subjects, brivaracetam is characterized by linear pharmacokinetics over a wide dose range (10–600 mg as a single dose and from 200 mg/day to 800 mg/day as multiple doses), with moderate inter-subject variability [19,20]. After single doses above 600 mg, a slightly more than dose-proportional increase in area under the plasma brivaracetam concentration versus time curve (AUC) has been observed. Steady state is reached within 1 week of repeated administration (Table 35.3).

Absorption

Brivaracetam is rapidly and almost completely absorbed, peak plasma concentrations being achieved after approximately 0.5–3 h following oral intake in the fasting state [19,20]. The drug is efficiently absorbed throughout the entire gastrointestinal tract, with a relative AUC (stomach = 100%) of 101%, 98% and 97% following delivery in the proximal jejunum, distal jejunum and ascending colon, respectively (UCB, data on file).

Co-administration with a high-fat meal resulted in a delayed median time to peak plasma concentration from 0.5 to 3.5 h post dose and a 28% reduction in peak plasma concentrations, while the extent of absorption (AUC) remained unchanged [19].

Single doses of an intravenous formulation of brivaracetam (10–150 mg) have been administered to healthy volunteers as either a 15-min infusion or a bolus dose of 10 mg/12 s [21]. Brivaracetam 10 mg administered as a 15-min intravenous infusion and as an intravenous bolus (10 mg/12 s) was bioequivalent to a single dose of brivaracetam 10 mg oral tablet. The pharmacokinetic parameters of brivaracetam (25 mg–150 mg) after intravenous infusion (15 min) and bolus (10 mg/12 s) were similar and dose proportionality was observed for each, from 25 to 150 mg.

Table 35.3 Plasma and urinary pharmacokinetic parameters after the first dose (day 1) and during a 12-h dosing interval on day 7 and day 14 of multiple dosing with brivaracetam 100 mg twice daily in nine healthy volunteers.

Parameter	Brivaracetam 100 mg twice-daily dosing		
	Day 1	Day 7	Day 14
C_{max} (μg/mL)	2.2 (14)	3.5 (22)	3.5 (20)
AUC (μg·h/mL)[a]	27.5 (23)	27.7 (21)	28.0 (24)
t_{max} (h)[b]	2 (1–4)	2 (1–3)	2 (1–2)
$t_{½}$ (h)	7.7 (20)	–	7.3 (26)
MRT (h)	11.8 (17)	–	10.9 (26)
CL/*F* (mL/min/kg)	0.83 (21)	0.83 (21)	0.83 (23)
V_z/F (L/kg)	0.55 (8.7)	–	0.51 (11)
$f_{e\ brivaracetam}$ (%)	4.6 (30)	5.1 (47)	5.7 (49)
$f_{e\ M9}$ (%)	16.5 (39)	17.6 (42)	22.3 (42)
$f_{e\ M1b}$ (%)	11.4 (62)	15.1 (66)	20.6 (55)
CL_R (mL/min/kg)	0.04 (30)	0.04 (42)	0.05 (39)

From ref. 20 with permission (Wiley-Blackwell Publishing).
Values are geometric means (CV%), unless stated otherwise.
AUC, area under the concentration versus time curve; CL/*F*, apparent plasma oral clearance; CL_R, renal clearance; C_{max}, peak plasma concentration; CV%, coefficient of variation of the geometric mean; f_e, fraction of the dose excreted in urine over 24 h (day 1) or over 12 h (days 7 and 14); MRT, mean residence time; $t_{½}$, half-life; t_{max}, time to peak plasma concentration; V_z/F, apparent volume of distribution. M1b and M9: metabolites as described in Fig. 35.2.
[a] AUC extrapolated to infinity after the first dose on day 1, AUC over 12-h dosing interval on days 7 and 14.
[b] Median (range).

Distribution

Brivaracetam is not extensively bound to plasma proteins (≤20%). The volume of distribution is 0.5 L/kg, a value that is close to the volume of distribution of total body water [22].

There is a strong correlation between brivaracetam saliva and plasma levels (r = 0.97, n = 241). The slope (standard error) is 0.88 (0.01), and closely corresponds to the free fraction of the drug in plasma as measured by equilibrium dialysis [20].

Elimination

In studies conducted in healthy volunteers, the elimination half-life of brivaracetam was found to be in the range of 6–11 h (mean, 7.7 h). The apparent oral clearance (CL/*F*) in these subjects is in the order of 0.7–0.9 mL/min/kg [19,20]. Following repeated administration, there is a modest time-dependent increase in metabolic clearance of brivaracetam at 800 mg/day with twice-daily administration, which is insignificant at 400 mg/day and below [20].

Brivaracetam is eliminated by hepatic metabolism and, to a much lesser extent (<10% of the dose), by direct urinary excretion (Fig. 35.2) [22]. Faecal excretion accounts for less than 1% of the dose. Excretion in expired air is undetectable. After administration of radiolabelled drug, the main circulating species is unchanged brivaracetam, amounting to 90% of the total plasma radioactivity [22]. The major metabolic pathways include hydrolysis of the acetamide group, hydroxylation mediated by several cytochrome P450 (CYP) enzymes (CYP2C19, CYP2C9, CYP3A4, with minor contributions of CYP2C8 and CYP2B6) and a combination of these (UCB, data on file). Although the renal clearance of the parent compound is low (about 0.04 mL/min/kg), its metabolites have a high renal clearance [20]. More than 95% of a radioactive dose is recovered in urine within 72 h, as the acidic (M9: 34.2% of the dose), ω-1 hydroxylated (M1b: 15.9%), and ω-1 hydroxylated acid (M4b: 15.2%) metabolites, and 8.6% as the parent drug (Fig. 35.2) [22]. There is no evidence of brivaracetam undergoing chiral inversion (i.e. conversion to other enantiomeric forms of the molecule). The hydrolysed metabolite and the two products of hydroxylation in the ω-1 position of the propyl chain are not pharmacologically active.

In a population pharmacokinetic study which utilized plasma concentrations obtained during two phase IIb adjunctive therapy studies in adult patients with refractory partial epilepsy, age, gender, race and creatinine clearance did not influence brivaracetam pharmacokinetic parameters. Differences in body weight and concomitant use of enzyme-inducing antiepileptic drugs (AEDs) accounted for most of the inter-individual variability, with an overall moderate influence on brivaracetam concentrations at steady state [23].

Pharmacokinetics in special populations

Elderly subjects

The pharmacokinetics of brivaracetam has been investigated in healthy elderly subjects after a 200-mg single dose and after

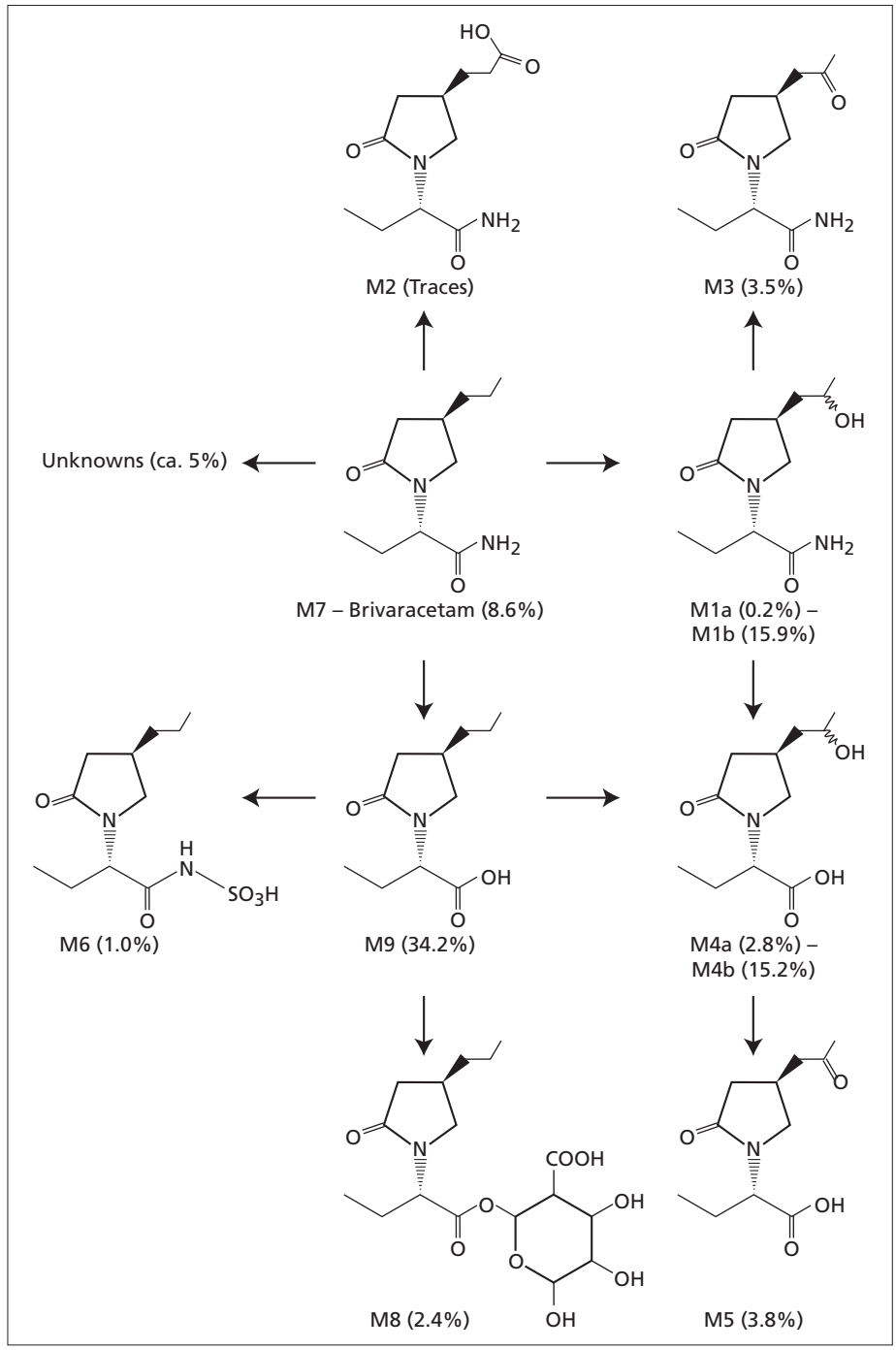

Fig. 35.2 Proposed metabolic pathways of brivaracetam in man following oral administration of a single 150-mg dose. Percentages in brackets refer to the mean fraction of the dose (%) recovered in urine within 48 h [22]. Forms 'a' and 'b' for metabolites M1 and M4 indicate occurrence of two stereoisomers at the position of the hydroxyl group [M1a and M4a (tentative) in 'up' position; M1b and M4b in 'down' position]. Reproduced from ref. 22 with permission (American Society for Pharmacology and Experimental Therapeutics).

200 mg twice-daily multiple dosing for 10 days [24]. After a single dose, absorption was rapid, with median time to peak plasma concentration occurring at 1.5 h. Plasma concentrations decayed monoexponentially, with a median half-life of 7.7 h (range 6.5–9.8 h) and 8.6 h (range 7.8–11.4 h) in the 65–75 years (n = 10) and >75 years (n = 6) groups, respectively. CL/F values (geometric means) at steady state were slightly lower in elderly males (0.74 mL/min/kg) than in young healthy males (0.83 mL/min/kg). The study concluded that these age-related pharmacokinetic differences are not expected to require dose adjustments in elderly patients.

Impaired renal function

The pharmacokinetics of a single oral dose of brivaracetam (200 mg) was investigated in nine severely renally impaired patients with a creatinine clearance (CL_{CR}) <30 mL/min/1.73 m^2, not requiring dialysis, in comparison with nine healthy subjects (UCB, data on file). Peak plasma brivaracetam concentrations

did not differ between patients with renal impairment and controls [mean ratio 99.7%; 90% confidence interval (CI) 85–117%] whereas total exposure as reflected by $AUC_{0-\infty}$ was slightly increased in the patients (mean ratio 121%; 90% CI 101–145%). The renal clearance of brivaracetam in the renally impaired group was reduced by 63% (from 4.48 to 1.66 mL/min/1.73 m^2). Peak plasma concentrations of the acidic, hydroxyl and hydroxy acid metabolites were increased 2.4-, 2.0- and 11.7-fold, and AUC values for the same metabolites were increased 3.2-, 4.1- and 21.5-fold, respectively. The renal clearance of these inactive metabolites was decreased 10-fold in renally impaired subjects compared with healthy controls. Overall, the modest increase in AUC of parent drug in the presence of renal impairment is unlikely to affect dose requirements, but cautious monitoring of clinical response to determine the possible need for dose adjustment is recommended if brivaracetam is prescribed in these patients. In the course of the clinical development of brivaracetam, it was identified that there were insufficient experimental toxicology data on the safety of the hydroxy acid metabolite, which accumulates at high concentrations in subjects with severe renal impairment. Therefore, the safety of the hydroxy acid metabolite was assessed in a battery of subsequent safety pharmacology studies in rodents and dogs (UCB, data on file). No adverse effects were observed on the CNS, gastrointestinal tract, or respiratory or cardiovascular systems. In the 14-day continuous intravenous infusion toxicity study in the Wistar rat, the hydroxy acid metabolite was of low toxicity, as demonstrated by very few findings observed after 14 days of treatment at doses up to 10 000 mg/kg/day. In this study there were no major differences between findings at 2000 and 10 000 mg/kg/day. At these high dose levels there were only small increases in kidney weights without any histological correlate and periportal hepatocellular degeneration without any modification of liver weight. A minor decrease in total white blood cell counts was observed at 10 000 mg/kg/day, mainly in male rats. No adverse effects were identified at the low dose of 500 mg/kg/day. Genotoxicity was evaluated *in vitro* in bacterial and mammalian cells and *in vivo* in rats. This hydroxy acid metabolite was neither mutagenic nor clastogenic. Although safety studies are not fully completed yet, based on already available findings it is not anticipated that longer-term exposure to this metabolite will result in any significant adverse effects.

Impaired hepatic function

A single oral 100-mg dose of brivaracetam was administered to 26 subjects stratified according to the Child–Pugh classification for mild (n = 6) moderate (n = 7) and severe (n = 7) hepatic impairment, and to six matched healthy controls. Plasma and urine concentrations of unchanged drug and metabolites were measured over 96 h [25]. The mean half-life of brivaracetam was 9.8 h, 14.2 h, 16.4 h and 17.4 h in healthy controls and in subjects with mild, moderate and severe hepatic impairment, respectively. Brivaracetam exposure in terms of AUC values (geometric means) was 29.7 μg/h/mL in healthy controls, and 44.6 μg/h/mL, 46.7 μg/h/mL, and 47.1 μg/h/mL in subjects with mild, moderate and severe hepatic impairment, respectively.

Compared with healthy control subjects, exposure to brivaracetam was increased by 50–60% in subjects with mild, moderate or severe hepatic impairment, without significant differences in relation to the degree of hepatic dysfunction. Exposure to the acid metabolite was increased by about 60–90% across Child–Pugh classes, whereas exposure to the hydroxy acid metabolite was increased 40–50% in the least liver-impaired subjects, only slightly increased in subjects with moderate impairment, and decreased by approximately 50% in the most severely affected. Exposure to the hydroxy metabolite decreased progressively by 40–80% with increasing hepatic dysfunction.

Overall, these findings indicate that the relative contribution of brivaracetam metabolic pathways is altered in subjects with hepatic impairment, with an increase in the formation of the acid metabolite and a decrease in the formation of the hydroxy metabolite. The adverse events reported in this study were mild to moderate, and their incidence was similar in the four groups. Dosage adjustments are not considered mandatory in patients with hepatic impairment, but a reduction in the starting and maintenance dosage may be considered on a case-by-case basis, also in relation to clinical response.

Drug interactions

Effect of other drugs on brivaracetam pharmacokinetics

In a population pharmacokinetic analysis of data from two adjunctive therapy studies in patients co-medicated with other AEDs, brivaracetam CL/*F* was estimated to be 5.15 L/h in the presence of enzyme-inducing AEDs compared with 3.63 L/h in the absence of enzyme inducers [23]. The difference is probably explained by stimulation of brivaracetam metabolism by enzyme-inducing AEDs such as carbamazepine, phenobarbital and phenytoin. Based on these data, enzyme-inducing AEDs would be expected to reduce plasma brivaracetam concentrations by about 30% and to shorten the brivaracetam half-life to approximately 5 h. However, a dose–response modelling, based on phase II data, has shown that concomitant enzyme-inducing AEDs did not affect the percentage of patients who are likely to respond or the extent of change in seizure frequency [26].

Preliminary data from CYP2C8 inhibition/induction studies indicated that repeated dosing with gemfibrozil 600 mg twice daily for 7 days had no significant effect on the plasma concentration of unchanged brivaracetam [27]. On the other hand, repeated administration of the enzyme inducer rifampicin 600 mg once daily for 8 days stimulated the biotransformation of brivaracetam via hydroxylation, decreased brivaracetam levels by 50% and shortened the brivaracetam half-life from 8.2 h to 4.5 h [27] (UCB, data on file).

Effect of brivaracetam on the pharmacokinetics of other antiepileptic drugs

Experiments conducted *in vitro* have shown that brivaracetam may inhibit epoxide hydrolase and, to a lesser extent, the CYP enzymes CYP3A4 and CYP2C19. In addition, it may induce weakly CYP3A4 [18].

In adjunctive therapy trials, brivaracetam (5–150 mg/day) did not cause any significant changes in the plasma concentration of concomitantly administered lamotrigine, levetiracetam, the mono-

hydroxy derivative of oxcarbazepine, valproic acid and topiramate [28].

In healthy volunteers, administration of brivaracetam 400 mg/day, which is at least four times above the dose expected to be required in patients with epilepsy, resulted in a slight (13%) reduction in the plasma levels of carbamazepine and a 2.5-fold increase in the levels of carbamazepine-10,11-epoxide [18]. The interaction is dose dependent: in patients with epilepsy, the carbamazepine-10,11-epoxide/carbamazepine ratio increased from 0.15 at baseline to 0.25, 0.31 and 0.44 at brivaracetam doses of 100, 200 and 400 mg/day, respectively (UCB, data on file). These changes in ratio are primarily ascribed to increases in the levels of carbamazepine-10,11-epoxide, since plasma carbamazepine concentration is not affected at brivaracetam doses below 400 mg/day.

Equivocal findings have been reported on the influence of brivaracetam on plasma phenytoin levels. In a formal interaction study in healthy volunteers who received single 600-mg doses of phenytoin in the absence and in the presence of concurrent treatment with brivaracetam (400 mg/day), a slight decrease in plasma phenytoin concentrations was observed during brivaracetam co-administration (UCB, data on file). However, in a study in patients with epilepsy on stable phenytoin therapy, addition of brivaracetam 400 mg/day resulted in an approximate 20% increase in phenytoin exposure at steady state (UCB, data on file). In a pooled analysis performed of data from phase II studies in patients with epilepsy, a similar increase in plasma phenytoin concentration by about 20% on average was observed after addition of brivaracetam at doses of 20 and 50 mg/day (UCB, data on file). In both the formal interaction study and the phase II studies, a high degree of inter- and intra-individual variability was observed, both between baseline measurements and under treatment. This is exemplified by a 2.3-fold increase in peak plasma phenytoin concentration in one patient in the formal interaction study, while in another subject peak concentration was reduced by 54%. Moreover, interpretation of the data from the phase II studies is made difficult by the small number of subjects who received phenytoin in these studies. In summary, the reason for the increase in phenytoin concentration being apparently unrelated to brivaracetam dose is unclear and larger patient numbers will be necessary for a better understanding of the relevance of the findings obtained so far.

Effect of brivaracetam on the pharmacokinetics of other drugs

Brivaracetam, given at the dosage of 400 mg/day, which is well above the highest dose investigated in phase II–III trials (150 mg/day), caused a moderate reduction of 20–30% in the extent of exposure and a 10–15% reduction in the peak plasma levels of ethinylestradiol and levonorgestrel in 24 healthy women receiving stable doses of an oral contraceptive (UCB, data on file). In the same study, there were no changes in the levels of estradiol, progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), or sex hormone-binding globulin (SHBG), and there was no evidence of ovulation. A second oral contraceptive study with brivaracetam 100 mg/day demonstrated an absence of interaction at that dose (UCB, data on file). Furthermore, continuation of brivaracetam dosing during the contraceptive-free week showed that trough levels of brivaracetam remained unchanged 1 week after interrupting the contraceptive.

Preliminary findings of a study aimed at assessing the effect of repeated brivaracetam administration at doses of 5, 50 and 150 mg/day over 1 week on CYP3A4 activity, using midazolam as a probe substrate, indicated the absence of induction of CYP3A4 activity by brivaracetam (UCB, data on file).

Serum level monitoring

There is currently no indication that monitoring plasma brivaracetam levels may aid in individualizing therapy, except for compliance assessment.

Efficacy

Proof-of-concept in photosensitive epilepsy

A single-blind, placebo-controlled phase IIa study assessed the effect of single doses of brivaracetam (10, 20, 40, or 80 mg) on the photoparoxysmal electroencephalographic response in 19 patients with photosensitive epilepsy [29]. Each patient received a single dose of placebo (day –1) and a single dose of brivaracetam (day 1) in the morning, at least 30 min after a light breakfast.

Of the 18 evaluable patients, none achieved complete abolishment of the photosensitivity response after placebo, compared with 78% after brivaracetam (Fig. 35.3). All subjects receiving the 80-mg dose of brivaracetam exhibited complete suppression of photosensitivity. The onset of drug action was fast (about 0.5 h after dosing), and its duration was twice as long after the 80-mg dose (59.5 h) as after lower doses. The area under the effect curve was linearly correlated with the area under the plasma concentration curve (Fig. 35.3).

Randomized controlled studies in refractory partial epilepsy

Two randomized, double-blind, placebo-controlled, adjunctive-therapy, parallel-group, phase IIb studies evaluated the efficacy and tolerability of different doses of brivaracetam in patients with refractory partial epilepsy receiving up to two concomitant AEDs [5,6]. Patients aged 16–65 years who had at least four partial-onset seizures, with or without secondary generalization, during a 4-week prospective baseline period were eligible for randomization. Prior or concomitant use of levetiracetam was permitted under the study protocols.

In study N01114, patients received placebo (n = 52) or brivaracetam 50 (n = 53) or 150 mg/day (n = 52) in two divided doses over a 3-week titration and a 7-week maintenance period. A statistically significant per cent reduction over placebo in weekly partial-onset seizure frequency during the 7-week maintenance period (primary efficacy variable) was not reached at either dose. Estimated per cent reductions over placebo were 14.7% (P = 0.093) and 13.6% (P = 0.124) for the 50 and 150 mg/day doses, respectively. However, a clear differentiation from placebo was observed for the 50 mg/day dose on several secondary efficacy analyses. In particular, a treatment effect was shown in weekly partial-onset seizure frequency per cent reduction from baseline (38.2%, P = 0.017, at 50 mg/day and 30.0%,

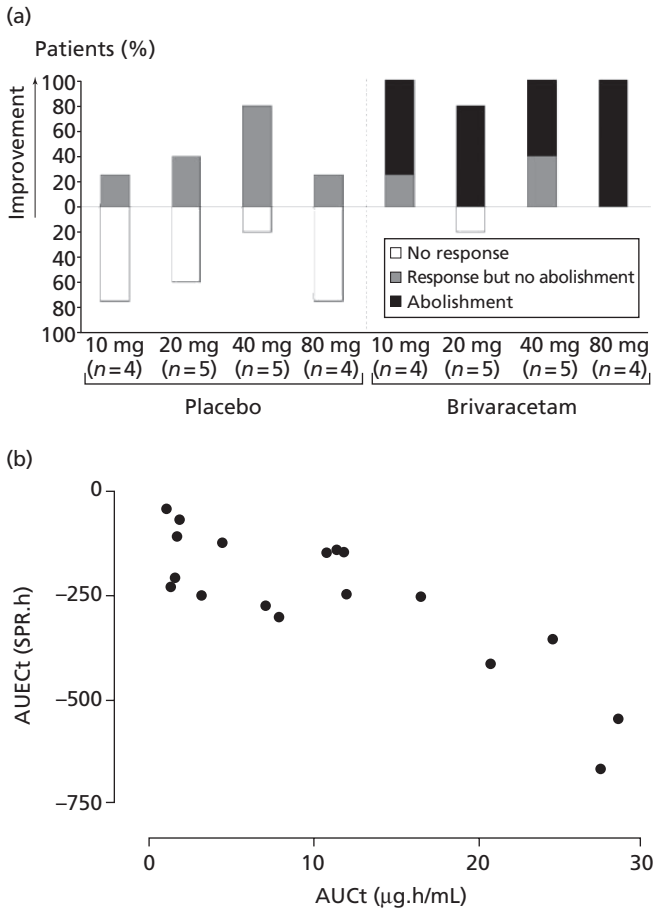

Fig. 35.3 Proof-of-concept placebo-controlled study of brivaracetam (single oral doses) in patients with photosensitive epilepsy. Reproduced from ref. 29 with permission from AAN Enterprises, Inc. (a) Standard photosensitivity range (SPR) response classification (comparison with pre-dose response) for the eye closure condition in relation to the administered dose of brivaracetam. Response = decrease of SPR by ≥3; abolishment, decrease of SPR to 0 at any tested time point. (b) Scatterplot of the area under the effect curve ($AUEC_t$, SPR change from pre-dose) versus area under the brivaracetam plasma concentration curve (AUC_t). Pearson $R = 0.82$; Spearman rho = 0.73.

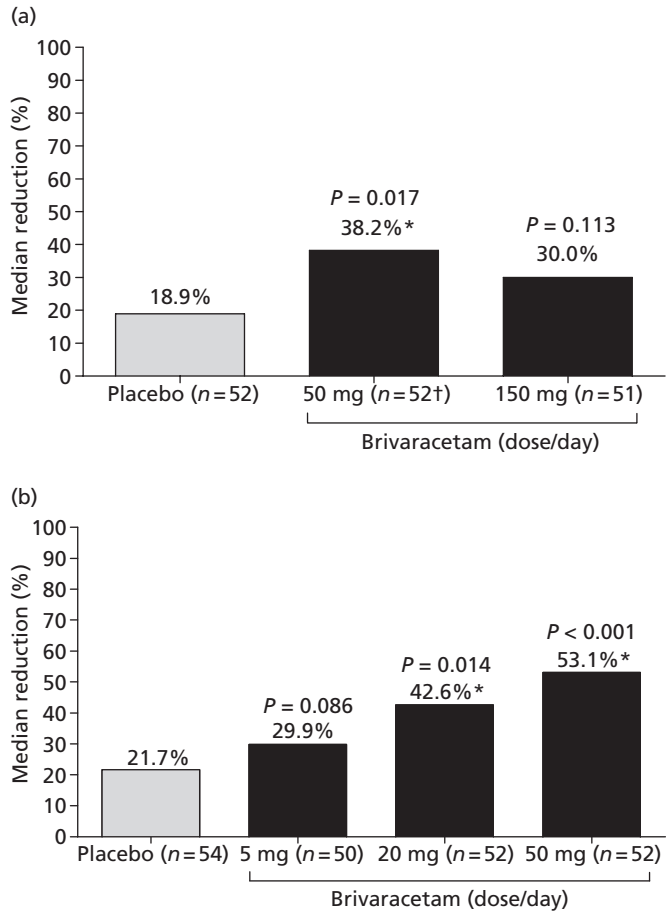

Fig. 35.4 Median per cent reduction in weekly partial-onset seizure frequency from baseline during the 7-week evaluation period in two adjunctive therapy randomized controlled trials of brivaracetam in patients with refractory partial epilepsy. (a) Study N01114 [6]. (b) Study N01193 [5]. *Statistically different from placebo; *P*-values are based on the Wilcoxon–Mann–Whitney test. †One patient had a seizure frequency of zero at baseline and reduction in partial-onset seizure frequency could not be evaluated in this patient.

$P = 0.113$, at 150 mg/day, compared with 18.9% on placebo) (Fig. 35.4a). Responder rates (percentage of patients with at least 50% reduction in seizure frequency compared with baseline) during the 7-week maintenance period were 39.6% and 33.3% in the 50 and 150 mg/day groups compared with 23.1% in the placebo group [6]. Estimated odds ratios (ORs) for responder rates (brivaracetam/placebo) were 2.16 ($P = 0.077$) at 50 mg/day and 1.66 ($P = 0.261$) at 150 mg/day (UCB, data on file). Thus, the higher brivaracetam dose (150 mg/day) did not appear to add therapeutic benefit. Freedom from partial-onset seizures during the entire 10-week treatment period was achieved in 9.4% of patients at 50 mg/day, 5.8% at 150 mg/day, and 1.9% on placebo [6].

In study N01193, patients received placebo ($n = 54$) or brivaracetam 5 ($n = 50$), 20 ($n = 52$) or 50 mg/day ($n = 52$) in two divided doses without titration for 7 weeks. The estimated per cent reduction in weekly partial-onset seizure frequency during the treatment period over placebo (primary efficacy variable) was 9.8% ($P = 0.240$) at 5 mg/day, 14.9% ($P = 0.062$) at 20 mg/day and 22.1% ($P = 0.004$) at 50 mg/day. This dose–response relationship was consistent with the results of secondary efficacy analyses. Per cent reduction in weekly partial-onset seizure frequency from baseline was 29.9% ($P = 0.086$) at 5 mg/day, 42.6% ($P = 0.014$) at 20 mg/day and 53.1% ($P < 0.001$) at 50 mg/day, compared with 21.7% on placebo (Fig. 35.4b). Responder rates were 32.0% at 5 mg/day (OR over placebo, 2.66; $P = 0.047$), 44.2% at 20 mg/day (OR, 4.27; $P = 0.002$) and 55.8% at 50 mg/day (OR, 7.21; $P < 0.001$), compared with 16.7% on placebo. Proportions of patients free from partial-onset seizures during the 7-week treatment period were 8.0%, 7.7% and 7.7% at 5, 20 and 50 mg/day, respectively, compared with 1.9% on placebo [5] (UCB, data on file).

Dose– and exposure–response modelling, based on the pooled data from the two studies, demonstrated a dose–response relationship for adjunctive brivaracetam therapy in 73% of patients, with an ED_{50} of 21 mg/day [26]. There was no improvement on switch-

ing from a dose–response to an exposure (plasma concentration)–response relationship. Age, body weight, gender, number of concomitant AEDs or the use of enzyme-inducing AEDs had no significant effect on the percentage of patients who improved or on the magnitude of the response.

Two randomized, double-blind, placebo-controlled, adjunctive therapy studies in adults with partial epilepsy (N01252, N01253; www.clinicaltrials.gov) will provide further information on the efficacy and safety of different doses of brivaracetam (20, 50 and 100 mg/day and 5, 20 and 50 mg/day, respectively) over a 12-week treatment period without titration. Several studies with brivaracetam are currently ongoing; two open-label extension studies in which patients from the phase II and phase III studies can continue to receive brivaracetam at flexible doses between 5 and 150 mg/day, and two conversion to monotherapy trials comparing brivaracetam at doses of 50 and 100 mg/day with a historical low-dose active control group, which are currently enrolling patients with uncontrolled partial-onset seizures (N01276, N01306; www.clinicaltrials.gov).

Randomized controlled studies in patients with other epilepsy syndromes

A double-blind, placebo-controlled, adjunctive therapy study (N01254; www.clinicaltrials.gov) will assess the safety and tolerability of brivaracetam in the dose range of 20–150 mg/day, in two divided daily doses, over a period of 16 weeks (8 weeks dose-finding and 8 weeks maintenance) in patients with inadequately controlled partial-onset or primary generalized seizures despite treatment with up to three concomitant AEDs.

Brivaracetam has received orphan drug designation in 2005 by the Food and Drug Administration for the treatment of symptomatic myoclonus, and by the European Medicines Agency for the treatment of progressive myoclonic epilepsies. Two randomized, double-blind, placebo-controlled, parallel-group studies of brivaracetam (5 and 150 mg/day in one study, 50 and 150 mg/day in the other, in two divided doses) as adjunctive treatment in 50 and 56 patients, respectively, with genetically ascertained Unverricht–Lundborg type progressive myoclonic epilepsy have been recently completed (N01187, N01236; www.clinicaltrials.gov). These patients suffered from moderate to severe action myoclonus and had failed, or were currently treated with, valproic acid and clonazepam. Previous and/or concomitant use of levetiracetam or piracetam was permitted. Both studies failed to reach the primary endpoint of reducing the severity of action myoclonus as measured by the Unified Myoclonus Rating Scale (UMRS).

Studies in other indications

The potential efficacy of brivaracetam (200 and 400 mg/day) in patients with postherpetic neuralgia has been assessed in a 4-week exploratory double-blind, randomized, placebo-controlled, parallel-group study (N01162, UCB, data on file). A total of 152 patients with pain for ≥6 months (pain scores ≥4 on an 11-point Likert scale) were included. In this trial, brivaracetam was well tolerated but did not show superiority to placebo in relieving the pain associated with postherpetic neuralgia.

Adverse effects

An overall safety analysis has been performed based on data from 18 phase I–IIa studies (UCB, data on file). A total of 327 subjects were included, of whom 112 received placebo and 318 received brivaracetam. The population included 201 healthy volunteers, 16 elderly volunteers, 81 subjects with epilepsy and 29 subjects with renal or hepatic impairment. Brivaracetam doses ranged between 10 and 1400 mg with single administration and between 200 and 800 mg/day following repeated administration in two divided daily doses. The maximal tolerated dose was 1000 mg after single doses, and was not reached (>800 mg/day) following multiple doses. The most commonly reported treatment-emergent adverse events (TEAEs) affecting ≥10% of patients were dizziness, somnolence, fatigue and headache. The median onset time of adverse events was ≤1 h and their duration appeared to be short. The incidence of adverse events decreased with subsequent administrations of brivaracetam. There was no indication of haematological or liver toxicity.

A further safety and tolerability evaluation was based on pooled data from the two phase IIb adjunctive therapy studies in patients with epilepsy [30]. Brivaracetam (5–150 mg/day) was overall well tolerated, and retention of patients was high in both studies (N01114: brivaracetam 95%, placebo 92%; N01193: brivaracetam 96%, placebo 91%). The proportion of patients with TEAEs was similar in the brivaracetam (all doses; 154/259, 59.5%) and the placebo (64/106, 60.4%) groups (Table 35.4). Adverse events leading to discontinuation of study medication occurred in eight brivaracetam patients (3.1%) and three placebo patients (2.8%). The most frequent TEAEs affecting ≥5% of patients are shown in Table 35.5. No significant difference in incidence was observed between the brivaracetam and the placebo groups for any of these events. No clinically significant changes in laboratory parameters or vital signs were observed in any treatment group.

Table 35.4 Summary of treatment-emergent adverse events (AEs) based on pooled data from brivaracetam randomized placebo-controlled phase IIb studies (N01114 and N01193).

	Brivaracetam, all doses (n = 259), n (%)	Placebo (n = 106), n (%)
Total number of AEs	376	168
Subjects with at least one AE	154 (59.5)	64 (60.4)
Subjects with AEs leading to discontinuation	8 (3.1)	3 (2.8)
Subjects with AEs leading to dose change	5 (1.9)	1 (0.9)
Subjects with drug-related[a] AEs	70 (27.0)	33 (31.1)
Subjects with severe AEs	6 (2.3)	5 (4.7)
Subjects with serious AEs	4 (1.5)	4 (3.8)
Subjects with drug-related[a] serious AEs	1 (0.4)	2 (1.9)

UCB, data on file.
AE, adverse event.
[a] Considered as at least possibly related to study medication by the investigator.

Table 35.5 Number of subjects with at least one treatment-emergent adverse event, based on data from brivaracetam randomized placebo-controlled phase IIb studies (N01114 and N01193).

	Brivaracetam <50 mg/day (*n* = 102), *n* (%)	Brivaracetam 50 mg/day (*n* = 105), *n* (%)	Brivaracetam 150 mg/day (*n* = 52), *n* (%)	Placebo (*n* = 106), *n* (%)
Gastrointestinal disorders				
Nausea	2 (2.0)	6 (5.7)	4 (7.7)	7 (6.6)
Vomiting	3 (2.9)	1 (1.0)	3 (5.87)	2 (1.9)
General disorders				
Fatigue	2 (2.0)	10 (9.5)	3 (5.8)	6 (5.7)
Infections/infestations				
Nasopharyngitis	1 (1.0)	7 (6.7)	4 (7.7)	4 (3.8)
Metabolic/nutrition disorders				
Anorexia	2 (2.0)	2 (1.9)	3 (5.8)	1 (0.9)
Nervous system disorders				
Convulsion	1 (1.0)	1 (1.0)	1 (1.9)	7 (6.6)
Dizziness	1 (1.0)	6 (5.7)	5 (9.6)	6 (5.7)
Headache	6 (5.9)	9 (8.6)	4 (7.7)	8 (7.5)
Somnolence	4 (3.9)	8 (7.6)	3 (5.8)	7 (6.6)
Psychiatric disorders				
Insomnia	1 (1.0)	2 (1.9)	3 (5.8)	1 (0.9)

UCB, data on file.
Only adverse events with an incidence of ≥5% in any treatment group are listed.

A randomized, double-blind, placebo- and positive-controlled thorough electrocardiographic study of multiple doses of brivaracetam in 182 healthy subjects to assess potential effects on the QT interval demonstrated the absence of any effects of brivaracetam on cardiac repolarization both at high therapeutic doses (150 mg/day) and at doses far in excess of those expected to be required in therapeutic use (800 mg/day) [31].

In the pharmacokinetic study of the intravenous solution, single brivaracetam doses ranging from 10 to 150 mg were well tolerated as 15-min infusions and as bolus injections (10 mg/12 s). All TEAEs were of mild or moderate severity, the most frequent (reported by ≥10% of patients) being headache, somnolence, fatigue, dizziness, feeling drunk and dysgeusia [21]. Physical examination, vital signs, electrocardiogram (ECG) and laboratory parameters showed no clinically significant abnormalities, and observed abnormalities in 24-h Holter ECG recordings were judged as not clinically significant and unrelated to the study drug by the investigator.

Place in current therapy

Since phase III studies have not been completed, at present there are insufficient data to determine the place of brivaracetam in epilepsy therapy. Phase II adjunctive therapy controlled trials in partial-onset seizures have shown that brivaracetam can be associated with high responder rates and excellent tolerability. If these results are confirmed in phase III studies, brivaracetam may prove a useful drug for the management of patients with refractory partial epilepsy. The possibility of initiating treatment with effective dosages without titration and with good tolerability would be particularly valuable features.

Brivaracetam shares with levetiracetam not only a similar structure, but also a common target at the SV2A binding site. Brivaracetam, however, has additional pharmacological actions not shared by levetiracetam, and in some animal models its effectiveness is superior to that of levetiracetam. Whether similar findings also apply in human epilepsy is unknown. In adjunctive therapy trials in partial epilepsy, levetiracetam-treated patients were not excluded, but the data available so far do not allow a conclusion on whether brivaracetam efficacy and tolerability are altered by previous or concomitant exposure to levetiracetam. Further data on this issue, and on the putative advantages of brivaracetam over levetiracetam, would be desirable. Additional areas where further data are required relate to brivaracetam's optimal dose range, and its spectrum of efficacy in different seizure types. While broad-spectrum efficacy is predicted by results in animal models, confirmation from controlled clinical studies in specific epilepsy syndromes is warranted.

The role of an AED in the therapeutic algorithm can only be defined after significant experience in the routine clinical setting has been acquired. While this is not yet the case with brivaracetam, results from the initial clinical trials indicate that this compound has promising features, which could contribute to its success for the treatment of epilepsy in the future.

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36 Carbamazepine

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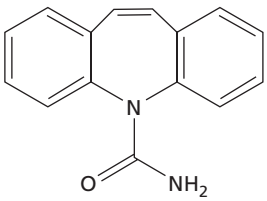

Primary indications	First-line or adjunctive therapy of partial and generalized tonic–clonic seizures
Usual preparation	Tablets: 100, 200, 400 mg; chewtabs: 100, 200 mg; sustained-release formulations: 200, 400 mg; suspension: 100 mg/5 mL; suppositories: 125, 250 mg
Usual dosages	Adults: starting dose is 100–200 mg/day, increased over 2–4 weeks to 400–600 mg/day. Maintenance dosages are usually in the range of 400–1600 mg/day (patients on concomitant enzyme inducers may require higher doses). Children: starting dose is up to 5 mg/kg/day, increased over 2–4 weeks to 10–20 mg/kg/day. Maintenance dosages are usually in the range of 5–30 mg/kg/day (10–40 mg/kg/day in infants)
Dosing frequency	2–4 times/day. Sustained-release formulations are usually administered twice daily
Significant drug interactions	Phenytoin and barbiturates decrease serum carbamazepine levels. Valproic acid and valpromide increase serum carbamazepine-10,11-epoxide levels. Felbamate decreases the serum levels of carbamazepine and increases the levels of carbamazepine-10,11-epoxide. Verapamil, erythromycin, dextropropoxyphene and many other drugs may increase carbamazepine levels. Carbamazepine is an enzyme inducer and stimulates the metabolism of many other antiepileptic drugs and drugs used to treat concomitant conditions. The central nervous system adverse effects of carbamazepine may be potentiated by lamotrigine and by oxcarbazepine
Serum level monitoring	Useful
Reference range	4–12 μg/mL (17–51 μmol/L)
Common/important adverse effects	Drowsiness, fatigue, dizziness, ataxia, diplopia, blurring of vision, dyskinesias, rash and other idiosyncratic reactions (including serious reactions affecting the bone marrow and other organs), hyponatraemia, cardiac dysrhythmias, decreased bone mineral density
Main advantages	Extensive clinical experience, highly effective and usually well tolerated
Main disadvantages	Transient adverse effects on initiating therapy. Occasional severe toxicity. Potential to precipitate or aggravate some generalized seizure types, particularly absence and myoclonic seizures. Enzyme-inducing effects and high drug interaction potential
Mechanism of action	Blockade of voltage-gated sodium channels
Oral bioavailability	75–85%. Bioavailability may be lower with sustained-release formulations

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Time to peak levels	4–8 h (or even longer, depending on formulation)
Elimination	Primarily metabolic through oxidation, hydroxylation, glucuronidation and sulphuration. Metabolism is mediated largely by cytochrome CYP3A4
Volume of distribution	0.8–2.0 L/kg
Elimination of half-life	At steady state, 5–26 h (very variable). Half-life is longer after a single dose and shortens during multiple-dose treatment due to autoinduction. Shortest half-life values occur in children and in patients co-medicated with enzyme inducers
Plasma clearance	At steady state, 1.06–3.59 L/h (very variable). Clearance is lower after a single dose and increases during multiple-dose treatment due to autoinduction. Highest clearance values occur in children and in patients co-medicated with enzyme inducers
Protein binding	75%
Active metabolites	Carbamazepine-10,11-epoxide
Comment	A drug of first choice for the treatment of partial seizures and generalized tonic–clonic seizures in children and adults

Introduction

The origin of carbamazepine dates back to the year 1899, when Thiele and Holzinger [1] described iminodibenzyl and its weak antiepileptic effect. This effect became substantially stronger when a carbamyl group was added at the 5 position of iminodibenzyl and combined with iminostilbene making a double bond between the 10 and 11 positions, resulting in a tricyclic compound which corresponds to carbamazepine. Since the mid-1960s, carbamazepine has been successfully used all over the world.

Chemistry

Carbamazepine corresponds chemically to 5H-dibenz(b,f)azepine-5-carboxamide. It is a white or yellowish-white, crystalline, odourless and tasteless powder. The molecular weight is 236.3. Carbamazepine is virtually insoluble in water, but soluble in absolute alcohol and benzene, chloroform, dichlormethane and other organic solvents. Its lipophilicity plays an important role in facilitating passage across biological membranes and barriers, including the blood–brain barrier.

The chemical structure of carbamazepine is similar to that of certain psychotropic drugs, such as imipramine, chlorpromazine and maprotiline. Carbamazepine may then be considered as a member of a family of polycyclic psychoactive drugs, and its activity in a number of psychiatric disorders, mainly as a mood stabilizer, has been clinically demonstrated. On the other hand, there are some features of its two-dimensional structure which are in common with certain antiepileptic drugs (AEDs) such as clonazepam, phenobarbital, phensuximide and phenytoin [2].

Pharmacology

The original studies of Theobald and Kuntz [3] in animal models revealed that carbamazepine shows potent activity against seizures induced by maximal electroshock, and a less potent effect in preventing experimental seizures induced by pentylenetetrazol. *In vitro* studies in hippocampal slices demonstrated that carbamazepine reduces burst firing in a calcium-free environment, implying a direct membrane effect, and not a direct neurotransmitter-mediated action [4]. Overall, the pharmacological profile of carbamazepine in animal models of seizures and epilepsy resembles that of phenytoin, and is predictive of activity against partial seizures and generalized tonic–clonic seizures [5]. Carbamazepine aggravates seizures in animal models of absence and myoclonic seizures, such as the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) [6].

The main action of carbamazepine is mediated through inhibition of voltage-activated sodium channels and, consequently, inhibition of action potentials and excitatory neurotransmission. High-frequency, repetitive neuronal firing is therefore limited [7]. The inhibitory potency is strongly dependent on use and accumulates with prolonged activation [5]. This is a classic mechanism of anticonvulsant action that is also shared by phenytoin, oxcarbazepine and, in addition to other mechanisms, by lamotrigine, zonisamide, topiramate and felbamate [5]. Some sodium channel blockers also have affinity for voltage-gated calcium channels, and inhibition of these channels may contribute to decrease excitatory neurotransmission. This mechanism is also important for the inhibitory effect exerted by some of these drugs on neuropathic pain [5,8].

Carbamazepine, like valproic acid, modulates intracellular signalling pathways which have been shown to be important in the

pathophysiology of bipolar disorder [9,10]. Many target proteins and signalling pathways may be involved in the clinical efficacy of carbamazepine and other mood stabilizers in bipolar disorder. Most studies conducted in this area are preclinical, and the effects of AEDs are usually compared with the effects on inositol concentrations by lithium [8]. Actions by carbamazepine and valproic acid on these proteins could explain their neurotrophic and neuroprotective properties that ameliorate impairments of cellular plasticity and resilience underlying the pathophysiology of mood disorders [11].

Pharmacokinetics

Absorption

The gastrointestinal absorption of carbamazepine is rather slow and variable, probably due to its slow dissolution in the gastrointestinal fluids. Peak serum concentrations are usually attained between 4 and 8 hours after oral administration of immediate-release tablets, but may be considerably longer depending on the formulation employed. The bioavailability of immediate-release tablets, chewable tablets swallowed whole and chewable tablets chewed before swallowing is estimated to be similar, in the order of 75–85% [12]. The bioavailability of many sustained-release formulations, however, is about 15–35% lower than that of immediate-release formulations, resulting in lower serum concentrations at steady state when patients are switched from immediate- to sustained-release dosage forms. Sustained-release formulations are also absorbed more slowly than immediate-release tablets and produce more stable serum drug concentrations during the day and at night, even when given twice daily, than immediate-release tablets given three times daily [13]. Conversely, oral suspensions are absorbed more rapidly and produce higher peak concentrations than tablets [12]. Food has not been shown to significantly affect the gastrointestinal absorption of carbamazepine [12].

Preparations of carbamazepine produced by different manufacturers may vary in bioavailability. To avoid the risk of breakthrough seizures or adverse effects, frequent changes in formulation are best avoided [14]. The bioavailability of moistured tablets is reduced up to 50% by storage of carbamazepine formulations in hot, humid conditions, which alter its form. Consequently, carbamazepine tablets should be stored in a dry, cool and dark place.

After rectal administration of a carbamazepine oral mixture, absorption appears to be significantly slower than after oral administration, but the overall bioavailability is similar provided that defecation does not occur during the first 2 hours. Rectal administration of suppositories has also been tested, and it has been suggested that it may need to be about 30% higher to compensate for lower bioavailability by this route [15].

Distribution

The apparent volume of distribution of carbamazepine varies reportedly from 0.8 to 2.0 L/kg in human adults. In neonates and infants it is 1.5-fold to 2-fold greater than in older children and adults.

Carbamazepine is highly bound (75–80%) to plasma proteins, including albumin and α_1-acid glycoprotein. A wider variation in binding is found in infants and children. The plasma protein binding of the active metabolite carbamazepine-10,11-epoxide is about 50% [13].

There is a significant positive correlation between brain and serum concentrations, with a ratio of about 1.1 for carbamazepine and 1.2–1.6 for carbamazepine-10,11-epoxide. There seems to be a non-specific binding of carbamazepine and carbamazepine-10,11-epoxide to brain tissue constituents [16].

Elimination

Only negligible amounts of carbamazepine are excreted unchanged in urine. Elimination occurs virtually entirely by metabolism. In the study of Faigle and Feldman [2], 72% of the radioactivity associated with a radiolabelled carbamazepine dose was detected in urine and 28% in the faeces.

Metabolic pathways include epoxidation, hydroxylation, glucuronidation and sulphuration. The main metabolic pathway is epoxidation, which is catalysed primarily by the cytochrome P450 enzyme CYP3A4 and results in the formation of carbamazepine-10,11-epoxide. This metabolite is pharmacologically active and accumulates in serum at clinically relevant concentrations, contributing to both therapeutic and adverse effects. Carbamazepine-10,11-epoxide is subsequently hydrolysed to the inactive metabolite trans-10,11-dihydroxy-carbamazepine.

Carbamazepine metabolism follows first-order kinetics and may vary considerably across subjects, resulting in a poor correlation between dose and serum concentration of both parent drug and its metabolites.

The metabolism of carbamazepine undergoes autoinduction. This is already detectable, but not fully expressed, by the second day after the first dose. In the first few weeks of treatment, autoinduction and the consequent increase in drug clearance cause a progressive decrease in serum carbamazepine concentrations, and increments in daily dosage may be needed to maintain the serum drug concentration within a given target range. Autoinduction is also dose dependent, i.e. drug clearance increases with increasing dosage and increasing serum drug concentration.

After a single dose, the half-life of carbamazepine varies between 20 and 65 h, but after autoinduction is completed (about 20–30 days after starting treatment), half-lives are in the range of 5–26 h for carbamazepine and 3–23 h for carbamazepine-10,11-epoxide.

Carbamazepine metabolism is also subject to heteroinduction by concomitantly administered enzyme-inducing antiepileptic drugs (AEDs) [2,12].

Relationship between serum concentration and dosage

Due to dose-dependent autoinduction, the pharmacokinetics of carbamazepine is non-linear, i.e. serum drug concentrations increase less than proportionally with each increment in dosage [17]. On the other hand, since the ratio of carbamazepine-10,11-epoxide to carbamazepine increases with increasing dosage, serum carbamazepine concentrations at higher dosages tend to underestimate the amount of pharmacologically active compound in blood.

Because of the relatively short half-life of carbamazepine under steady-state conditions, serum carbamazepine concentrations may show marked fluctuations during a dosing interval, with high peak plasma concentrations, which may result in intermittent

adverse effects. Fluctuations are particularly marked in children and in patients co-medicated with enzyme inducers, and may be minimized by more frequent daily administration or by use of a sustained-release formulation.

Pharmacokinetics in special groups

Children

The bioavailability of carbamazepine is similar in children and adults, but in infants the extent of absorption may be reduced and more variable. The bioavailability of carbamazepine may be reduced greatly by malabsorption states, and protein–energy malabsorption in particular. The volume of distribution of carbamazepine is 1–1.5 times higher in infants than in children and adults.

In children, there is a wide variation in carbamazepine clearance and half-life, in relation to the child's age, co-medication and duration of treatment. The carbamazepine-10,11-epoxide to carbamazepine ratio also varies widely, but increases with increasing dosage and decreases progressively with age. Higher clearance rates are correlated with early childhood years, small body mass, high daily dosage and male gender. Diurnal fluctuations in serum carbamazepine concentrations are also greater in children than in adults, and to minimize adverse effects associated with high peak plasma levels a sustained-release formulation is often used in children able to take solid medications [12].

Elderly

Both autoinduction and heteroinduction by enzyme-inducing AEDs are retained in the elderly, but the lower metabolic rate results in moderately decreased carbamazepine clearance in elderly subjects compared with non-elderly adults [18]. This, together with an increased sensitivity to the effects of carbamazepine in old age, contributes to dosage requirements being lower in the elderly than in the young.

Pregnancy

During the first trimester, serum carbamazepine concentrations are reportedly reduced compared with the prepregnant state, but the data are controversial. Total serum carbamazepine concentrations may be lower toward the end of pregnancy, but changes in unbound serum concentrations are generally less prominent. Overall, clinically significant changes in carbamazepine pharmacokinetics do not appear to be common during pregnancy, although in occasional patients dosage adjustments may be needed [19–21].

The cord blood–maternal concentration ratio of carbamazepine ranges from 0.5 to 0.8. The fetal brain to serum ratio is similar to that observed in adults, probably due to the fact that both carbamazepine and carbamazepine-10,11-epoxide are easily transferred to fetal tissues. The carbamazepine half-life in neonates of mothers on continuing carbamazepine medication has been reported to range from 8.2 to 27.7 h [12].

Breastfeeding

There is a wide variation in milk to serum carbamazepine concentration ratio, with a range of 0.15–0.80. Full-term neonates of normal birth weight (3000–3500 g) born to mothers receiving carbamazepine medication have been estimated to receive a dose of 0.5–0.7 mg/kg through breast milk. Mothers taking carbamazepine may breastfeed their infants, provided that the infant is observed for possible adverse effects (e.g. excessive somnolence or skin rashes). Monitoring of serum carbamazepine concentrations in breastfed infants is not mandatory. Very rare cases of neonatal transient hepatic dysfunction have been reported [22].

Hepatic disease

Mild or moderate liver dysfunction does not affect carbamazepine metabolism. However, a decrease in plasma protein binding may occur. More severe dysfunction may result in decreased carbamazepine clearance [12].

Other diseases

In patients with renal disease, no significant changes in carbamazepine pharmacokinetics have been noted. In heart failure, the congestion of major vital organs may result in slower absorption [12].

Drug interactions

Drug interactions with carbamazepine are common. Since carbamazepine is primarily metabolized by CYP3A4, concomitant medications that induce or inhibit CYP3A4 may have prominent effects on carbamazepine clearance and modify significantly serum carbamazepine concentrations at steady state. Carbamazepine itself is a potent inducer of drug-metabolizing enzymes, and by this mechanism it affects in an important way the pharmacokinetics of many concomitantly administered drugs [23–25].

If interacting co-medications cannot be avoided, careful observation of clinical response and, whenever appropriate, monitoring of serum drug concentrations will aid in minimizing potentially adverse clinical consequences [25].

Interactions between carbamazepine and other AEDs

Interactions resulting in altered serum concentration of carbamazepine or altered carbamazepine response

Serum carbamazepine concentrations are lowered by combination therapy with phenobarbital, phenytoin, primidone, oxcarbazepine and felbamate (Table 36.1).

Valproic acid, valpromide and felbamate may cause an increase in the concentrations of carbamazepine-10,11-epoxide. An increase in serum concentration of carbamazepine-10,11-epoxide has been reported occasionally after addition of lamotrigine, but such interaction has not been confirmed in most studies. The appearance of central nervous system (CNS) adverse effects, which is sometimes observed following addition of lamotrigine in carbamazepine patients, appears to mainly be due to a pharmacodynamic drug interaction [23–25].

Carbamazepine metabolism does not appear to be affected by gabapentin, levetiracetam, pregabalin, tiagabine, topiramate or vigabatrin.

Interactions resulting in altered serum concentration of the other AEDs

Carbamazepine stimulates the rate of metabolism of most co-administered AEDs, including valproic acid, tiagabine,

Table 36.1 Effect of other antiepileptic drugs on serum concentrations of carbamazepine.

Increased concentration	Decreased concentration	No effect
Stiripentol	Felbamate[b]	Ethosuximide
Valproic acid[a]	Phenobarbital	Gabapentin
Valpromide[a]	Phenytoin	Lamotrigine[c]
	Primidone	Levetiracetam
	Oxcarbazepine	Pregabalin
	Rufinamide (minor effect)	Topiramate
		Tiagabine
		Vigabatrin[d]
		Zonisamide[d]

Modified from refs 23, 25 and 26.
[a] Little effect on serum carbamazepine concentration, but marked increase in serum carbamazepine-10,11-epoxide, particularly with valpromide.
[b] The decrease in serum carbamazepine concentration is associated with an increase in serum carbamazepine-10,11-epoxide.
[c] Possible appearance of neurotoxic effects may be related to a pharmacodynamic interaction.
[d] Variable effects have been reported in some studies.

ethosuximide, lamotrigine, topiramate, oxcarbazepine and its monohydroxy derivative, zonisamide, felbamate, rufinamide, many benzodiazepines and, to some extent, levetiracetam [23–25]. The clinical significance of these interactions is usually modest because the consequences of the reduction in serum level of the affected AED are compensated for by the added pharmacological effect of carbamazepine. However, in some cases, seizure control may be adversely influenced. Dosage adjustments of the AED affected by the interaction are most commonly required for valproic acid, lamotrigine and tiagabine, because the decrease in the serum concentrations of these drugs after adding carbamazepine can be quite prominent (50–75%).

Particular caution is required when carbamazepine is withdrawn from the therapeutic regimen of patients taking co-medications, the metabolism of which have been increased by carbamazepine. In fact, the concentration of these drugs may increase to toxic levels after removal of carbamazepine, unless their dosage is adjusted appropriately. This is especially true for valproic acid, lamotrigine and tiagabine.

The effects of carbamazepine on the pharmacokinetics of phenobarbital and primidone are somewhat variable (Table 36.2). In patients on primidone, carbamazepine may decrease the serum levels of primidone and increase those of metabolically derived phenobarbital.

Interactions between carbamazepine and other drugs

Interactions resulting in altered serum concentrations of carbamazepine

Many drugs other than AEDs affect carbamazepine metabolism (Table 36.3). Several drugs, including known inhibitors of CYP3A4, can precipitate signs of carbamazepine toxicity by increasing serum carbamazepine concentrations [23–25]. This needs to be taken into consideration when selecting drugs within a given pharmacological class: for example, clarithromycin, tro-

Table 36.2 Effects of carbamazepine on the serum concentrations of other antiepileptic drugs.

Increased concentration	Decreased concentration	Variable (increase, decrease or no change)	No effect
Phenobarbital metabolically derived from primidone	Clobazam	Phenytoin	Gabapentin
	Clonazepam	Phenobarbital	Pregabalin
	Diazepam		Vigabatrin
	Ethosuximide		
	Felbamate		
	Lamotrigine		
	Levetiracetam		
	Midazolam		
	Oxcarbazepine[a]		
	Primidone		
	Rufinamide		
	Stiripentol		
	Tiagabine		
	Topiramate		
	Valproic acid		
	Zonisamide		

Modified from refs 23, 25 and 26.
[a] Monohydroxymetabolite.

Table 36.3 Effect of other drugs on serum concentrations of carbamazepine.

A Drugs causing an increase in serum carbamazepine concentration

Antidepressants
Fluoxetine
Fluvoxamine
Nefazodone
Trazodone
Viloxazine

Antimicrobials
Clarithromycin
Erythromycin
Fluconazole
Isoniazid
Ketoconazole
Metronidazole
Ritonavir
Troleandomycin

Miscellaneous
Cimetidine
Danazol
Dextropropoxyphene
Diltiazem
Risperidone
Quetiapine
Ticlopidine
Verapamil

B Drugs causing a decrease in serum carbamazepine concentration

Probenecid
St John's wort

Modified from refs 23 and 25.

leandomycin and erythromycin increase serum carbamazepine concentrations markedly and should be preferably avoided in patients taking carbamazepine, whereas other macrolides such as azithromycin, dirithromycin, rokitamycin and spiramycin do not inhibit CYP3A4 and can be given safely to carbamazepine-treated patients [26]. Grapefruit juice may also inhibit CYP3A4, and has a modest elevating effect on serum carbamazepine concentrations.

Interactions whereby other drugs decrease serum carbamazepine levels are less common. Probenecid appears to reduce the serum concentration of carbamazepine by increasing its biotransformation to carbamazepine-10,11-epoxide [27]. St John's wort may also reduce serum carbamazepine concentrations.

Interactions resulting in altered serum concentrations of other drugs

Carbamazepine induces the metabolism of many other drugs, including steroids (including hormonal contraceptives), oral anticoagulants, ciclosporin A, many anti-cancer agents and many psychotropic drugs (Table 36.4).

Most of these interactions are clinically significant [23–25]. The interaction is greatest with drugs which undergo significant first-pass metabolism, such as itraconazole, praziquantel, indinavir and most dihydropyridine calcium antagonists. In enzyme-induced patients the serum concentration of these drugs may decrease 5- to 10-fold, and the practical management of these patients may be very difficult. Drug interactions involving oral contraceptives, oral anticoagulants, immunosuppressants and chemotherapeutic agents may have serious consequences when they result in therapeutic failure of the affected drug [25]. If the dosage of the affected drug has been increased to compensate for its enhanced clearance, serious consequences may also arise when carbamazepine therapy is withdrawn. In that situation, the serum concentration of the affected drug may increase to toxic levels, unless dosage is carefully readjusted.

In some instances, when the affected drug is converted to toxic metabolites, enzyme induction by carbamazepine may result in potentiation of toxicity rather than in reduced pharmacological effect. A possible example is provided by some evidence that the concomitant use of carbamazepine and isoniazid may increase isoniazid-induced liver toxicity, putatively due to accelerated production of hepatotoxic isoniazid metabolites.

Table 36.4 Effects of carbamazepine on the serum concentrations of other drugs.

Decreased concentration

Antidepressants	*Antimicrobials*	*Antipsychotic drugs*
Amitriptyline	Albendazole	Chlorpromazine
Bupropion	Doxycycline	Clozapine
Citalopram	Indinavir	Haloperidol
Clomipramine	Itraconazole	Mesoridazine
Desipramine	Metronidazole	Olanzapine
Desmethylclomipramine	Praziquantel	Quetipine
Doxepin		Risperidone
Imipramine		Ziprasidone
Mianserin		
Mirtazepine		
Nefazodone		
Nortriptyline		
Paroxitine		
Protriptyline		
Immunosupressants	*Steroids*	*Miscellaneous*
Ciclosporin A	Dexamethasone	Fentanyl
Sirolimus	Hormonal contraceptives	Meperidine
Tacrolimus	Hydrocortisone	Methadone
Oral anticoagulants	Methylprednisolone	Metyrapone
Dicoumarol	Prednisone	Misonidazole
Warfarin	Prednisolone	Paracetamol
		Theophylline
		Thyroxine
		Vecuronium

Modified from refs 23 and 25.

Pharmacodynamic interactions between carbamazepine and other drugs

The combination of lithium and carbamazepine may cause enhanced neurotoxic effects in spite of serum lithium concentrations remaining within the therapeutic range. This interaction is probably pharmacodynamic in nature.

Because carbamazepine is structurally related to tricyclic antidepressants, the use of carbamazepine in combination with monoamine oxidase inhibitors (MAOIs) is not recommended. Before administering carbamazepine, MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.

Concomitant medication of carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium). Although pharmacokinetic effects may contribute to this interaction, a pharmacodynamic mechanism is probably also involved. The dosage of non-depolarizing muscle relaxants may need to be raised and patients should be monitored closely for a more rapid recovery from neuromuscular blockade than expected.

Carbamazepine, like other psychoactive drugs, may potentiate the CNS depressant effects of ethanol.

Serum level monitoring

There are no prospective controlled trials that define therapeutic concentrations for carbamazepine, as is the case for most other AEDs [28]. Studies, however, suggest that most patients optimally treated with carbamazepine have serum concentrations in the order of 4–12 μg/mL (17–51 μmol/L) [29]. The optimal concentration may be lower in patients on co-medication with other AEDs. There is, in any case, a considerable overlap between serum carbamazepine concentrations in well-controlled patients and those with adverse effects.

Carbamazepine has a narrow therapeutic index, and the relationship between dose and carbamazepine concentration is unpredictable. In addition, the susceptibility of carbamazepine metabolism to important drug interactions supports the need to individualize carbamazepine treatment using therapeutic drug

monitoring. Since carbamazepine has a relatively short half-life, sampling time in relation to dose ingestion is important. Ideally, blood samples should be drawn before the morning dose, but in some situations (e.g. in patients with intermittent adverse effects) separate determinations both at the time of trough and at the expected time of peak may be desirable. Carbamazepine-10,11-epoxide is not routinely measured, though there are patients in whom high concentrations of this metabolite can be responsible for otherwise unexplained toxicity [29].

Efficacy

Carbamazepine is indicated for the treatment of partial-onset and generalized tonic–clonic seizures but not for absence, myoclonic and most other generalized seizure types. Its efficacy has been evaluated in a large number of clinical trials including patients of different ages, with inclusion criteria usually based on seizure type rather than epilepsy syndrome.

Partial-onset seizures

Other than phenytoin, carbamazepine is the only AED considered to be established as efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures by the criteria of the Commission of Therapeutic Strategies of the International League against Epilepsy (ILAE) level A recommendation [30]. No other drug has been shown to be more effective than carbamazepine for this indication in randomized controlled trials. Carbamazepine is therefore established as standard treatment for partial-onset seizures in adults and represents an adequate reference for comparative trials according to the ILAE criteria [30]. In fact, there have been many double-blind and open-label randomized controlled studies which compared the efficacy of carbamazepine and other AEDs in patients with partial-onset seizures of different ages.

Adults

In the Veterans' Affairs multicentre double-blind study carried out in the USA, 622 adults with previously untreated or undertreated partial and secondary generalized seizures were randomized to carbamazepine, phenobarbital, phenytoin or primidone [31]. The follow-up period was 2 years or up to withdrawal for lack of efficacy or adverse effects. Overall success rates in terms of retention on the allocated treatment were highest with carbamazepine and phenytoin, intermediate with phenobarbital and lowest with primidone. Carbamazepine provided complete control of all partial seizures more often than primidone or phenobarbital. Carbamazepine was subsequently compared with valproic acid using a similar methodology [32]. In total, 480 adults with previously untreated or undertreated partial-onset seizures were randomized. Seizure freedom rates were similar at 1 and 2 years' follow-up, although patients with predominantly complex partial seizures did significantly better with carbamazepine in terms of time to first seizure. Another double-blind randomized trial compared carbamazepine and vigabatrin in 459 patients, aged 12–65 years, with newly diagnosed partial-onset seizures [33]. Seizure freedom at 1 year was significantly higher with carbamazepine (58%) than with vigabatrin (38%), although vigabatrin was better tolerated. In a more recent double-blind trial using a non-inferiority design, adults with newly diagnosed partial-onset or generalized tonic–clonic seizures (but excluding patients with clinical or EEG features suggestive of idiopathic generalized epilepsy) were randomized to controlled-release carbamazepine (400–1200 mg/day, $n = 285$) or levetiracetam (1000–3000 mg/day, $n = 291$) [34]. Approximately 80% in each treatment group were considered to have partial-onset seizures. The two drugs were equally effective, with 73% seizure free for at least 6 months at the last evaluated dose in the per-protocol analysis. Of those achieving remission on carbamazepine, 85% did so at the lowest dose level (400 mg/day). The proportion of patients seizure free and the time to first seizure were similar for carbamazepine (immediate-release tablets) and lamotrigine in a double-blind randomized trial including 260 newly diagnosed adult patients with partial-onset or generalized tonic–clonic seizures, but in this trial more patients on carbamazepine withdrew because of adverse events [35]. Topiramate, 100 mg/day or 200 mg/day, was compared with carbamazepine, 600 mg/day, in a double-blind randomized study of 390 newly diagnosed patients for whom the treating physician considered carbamazepine to be standard treatment [36]. Approximately 75% of these patients had partial-onset seizures. No significant difference was observed in efficacy measures. Carbamazepine was also compared with oxcarbazepine in a double-blind randomized study including 235 patients with newly diagnosed partial-onset or generalized tonic–clonic seizures [37]. Similar proportions were seizure free on carbamazepine (60%) and oxcarbazepine (52%) during the 48-week maintenance phase, but more patients on carbamazepine were withdrawn because of skin rashes.

Among open-label randomized studies, SANAD [38] is by far the largest. In this study, 1721 patients with epilepsy, for whom carbamazepine was deemed to be preferable to valproate as an initial treatment choice, were randomized to carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. Of the randomized patients, 88% were considered to have symptomatic or cryptogenic partial epilepsy. For time to 12-month remission carbamazepine was significantly better than gabapentin and had a non-significant advantage over lamotrigine, topiramate and oxcarbazepine. However, lamotrigine was significantly better than carbamazepine with respect to time to treatment failure. This advantage was mainly explained by fewer withdrawals for adverse events with lamotrigine. Reported differences in tolerability need to be interpreted with some caution in open-label studies. Selection of an unnecessarily high target dose and use of immediate-release rather than sustained-release carbamazepine tablets in an unknown proportion of patients could also have contributed to a poorer tolerability of carbamazepine in this study.

Other open-label randomized studies have compared carbamazepine with valproate, phenytoin and phenobarbital in patients with either partial-onset or primary generalized tonic–clonic seizures. In one of these studies, 300 adults with newly diagnosed seizures (about half with partial-onset seizures) were randomized to either carbamazepine or valproate [39]. In the partial-onset seizure group, 12-month remission rates were similar (72% for valproate and 76% for carbamazepine). In another open-label study, Heller *et al.* [40] randomized 243

adults with previously untreated tonic–clonic or partial-onset seizures (n = 102) to phenobarbital, phenytoin, carbamazepine or valproate. No significant differences were found for efficacy measures at 1, 2 or 3 years of follow-up. Although results were not presented for partial-onset seizures separately, the authors found no interaction between the drugs and seizure type on the outcome.

The elderly

The efficacy of carbamazepine in elderly patients with newly diagnosed epilepsy has been assessed in three double-blind randomized comparative trials [41–43]. Brodie *et al*. [41] randomized 150 patients aged 65 years and above to immediate-release carbamazepine (n = 48) or lamotrigine (n = 102). Withdrawals due to adverse events were more common with carbamazepine (42%) than with lamotrigine (18%), but there was no difference between the two drugs in time to first seizure. Because of fewer drop-outs due to poor tolerability, a greater percentage of lamotrigine-treated patients remained seizure free during the last 16 weeks of the 24-week treatment duration (39%, compared with 21% in the carbamazepine group). A large US study randomized 593 patients aged 60 years and over to either immediate-release carbamazepine (target dose 600 mg/day), lamotrigine (150 mg/day) or gabapentin (1500 mg/day) [42]. The primary outcome measure was retention in the trial for 12 months. There were no significant differences in seizure-free rates at 12 months among those remaining in the study (64% with carbamazepine, 51% with lamotrigine and 47% with gabapentin). However, early termination for adverse events was more common with carbamazepine (31%) than with lamotrigine (12%). The latest study compared flexible-dosage sustained-release carbamazepine with lamotrigine in 185 newly diagnosed patients, 65 years or older, with partial-onset or generalized tonic–clonic seizures [43]. Similar percentages of patients completed the 40-week study period, 67% with carbamazepine and 73% with lamotrigine. The proportion completing the study and seizure free in the last 20 weeks was also similar, 57% with carbamazepine and 52% on lamotrigine. Adverse events leading to withdrawal occurred in 14% of patients in the lamotrigine group and 25% in the carbamazepine group. Overall, the tolerability of carbamazepine was more favourable in this trial using a sustained-release formulation than in the other two trials.

Children

By the criteria of the ILAE Commission on Therapeutic Strategies, there are no class I or II randomized controlled trials of carbamazepine in children with partial-onset seizures. A double-blind randomized trial compared carbamazepine 600 mg/day with valproate 1250 mg/day or topiramate 100 or 200 mg/day in newly diagnosed epilepsy (patients with partial-onset seizures in the majority of cases) [36]. In the paediatric subgroup of patients with partial-onset seizures, time to exit (primary outcome measure) was similar for the different treatment arms. Two open-label randomized trials compared carbamazepine with other old-generation AEDs in children with newly diagnosed partial-onset and primary generalized tonic–clonic seizures. In the first of these trials, Verity *et al*. [44] randomized children to valproate (n = 130) or carbamazepine (n = 130) and followed them up for 3 years. Carbamazepine and valproate showed similar efficacy in controlling both primary generalized seizures and partial-onset seizures with or without secondary generalization. Adverse effects were mild and necessitated drug withdrawal in only a few children. In the second study, 167 children aged 3–16 years, with tonic–clonic or partial seizures, were randomly allocated to treatment with phenobarbital (n = 10; assignment to this group was stopped after adverse effects occurred in six of the first 10 randomized children), phenytoin (n = 54), carbamazepine or valproate (n = 49) [45]. Overall, 73% of patients achieved 1-year remission by 3 years of follow-up, with minor differences between the three assessed drugs. There seemed to be no effect of the type of seizures on the outcome. Among the drugs for which randomization was allowed until completion of the study, phenytoin was more likely to result in withdrawal (9%) than carbamazepine (4%) or valproate (4%).

Primary generalized tonic–clonic seizures

In addition to partial seizures, carbamazepine is approved by many regulatory agencies for the treatment of primary generalized tonic–clonic seizures. Nevertheless, documentation in terms of double-blind randomized clinical trials in this indication is sparse. By the criteria of the ILAE Commission on Therapeutic Strategies, there are no class I or II randomized controlled trials demonstrating the efficacy of carbamazepine (or any other AED) in the treatment of generalized tonic–clonic seizures in adults or children. In fact, there are no double-blind randomized monotherapy studies specifically targeting patients with primary generalized tonic–clonic seizures. The best available evidence is derived from trials in which such patients constitute a subset of the included population, and results are difficult to interpret not only because of the small sample sizes but also because of the possibility that in some patients secondary generalized seizures without an evident focal onset may have been erroneously classified as primary generalized.

Similar proportions of patients in each group were seizure free in the subset of adults with generalized tonic–clonic seizures included in the double-blind randomized trial comparing carbamazepine with oxcarbazepine [37]. Likewise, the same percentage of patients on carbamazepine and lamotrigine became seizure free and were retained on treatment in the subgroups with generalized tonic–clonic seizures included in a trial that enrolled mostly patients with partial-onset seizures [35]. Similar proportions of the paediatric and adult patients with generalized tonic–clonic seizures were seizure free in the last 6 months of treatment in the trial comparing carbamazepine, valproate and two different dosages of topiramate [36].

Open-label randomized trials including mixed groups of patients with partial-onset and generalized tonic–clonic seizures have compared carbamazepine with phenytoin and valproate [46], with valproate only [39], and with phenytoin and valproate [40]. In the study by Callaghan *et al*. [46] comprising a total of 181 patients, a reduction by 51% to 100% in seizure frequency in the subgroup with primary generalized tonic–clonic seizures was reported in 75% of patients on carbamazepine compared with 81% and 78% of patients on phenytoin and valproate, respectively. Significantly more patients with generalized convulsive seizures became seizure free with phenytoin than

with carbamazepine [46]. In another trial comparing carbamazepine and valproate in mixed seizure types, there was no difference between the two treatments in 12-month remission rates in the subset of 138 patients with primary generalized tonic–clonic seizures [39]. In a third trial, in which seizure outcome was not reported separately for partial-onset and for generalized tonic–clonic seizures, seizure control did not differ significantly among the groups randomized to carbamazepine, phenytoin and valproate [40].

A meta-analysis based on class III evidence concluded that there is no reliable evidence to differentiate in efficacy carbamazepine from valproate in patients with primary generalized tonic–clonic seizures [47]. Another meta-analysis found no significant differences between carbamazepine and phenytoin for outcomes examined for generalized tonic–clonic seizures [48].

Although the available evidence suggests that carbamazepine is effective in the treatment of primary generalized tonic–clonic seizures, it should be borne in mind that other data suggest that carbamazepine precipitate or aggravate other generalized seizure types, particularly absence and myoclonic seizures, in patients with generalized epilepsy syndromes [49,50]. It appears that even primary generalized tonic–clonic seizures can be sometimes aggravated in a subset of patients with idiopathic generalized epilepsies.

Epilepsy syndromes

Benign epilepsy with centrotemporal spikes

Carbamazepine has not been assessed in randomized clinical trials in the treatment of benign epilepsy with centrotemporal spikes. Nevertheless, it is often used if treatment is considered for this indication, based on its proven efficacy in patients with partial-onset seizures in general [30].

Idiopathic generalized epilepsies

Although carbamazepine can be effective in the treatment of generalized tonic–clonic seizures, it is generally avoided when these seizures occur in the context of childhood or juvenile absence epilepsy or juvenile myoclonic epilepsy, due to the risk of precipitating or aggravating absences and myoclonic seizures. Carbamazepine may even precipitate non-convulsive status epilepticus in these patients [49].

Symptomatic generalized epilepsies

Trials with carbamazepine are hardly successful if corticotropin, valproate or vigabatrin have failed. In some patients with symptomatic myoclonic–astatic epilepsy or Lennox–Gastaut syndrome, carbamazepine can improve at least temporarily seizure control, usually when used in combination with other AEDs.

Combination therapy

Carbamazepine is often combined with other AEDs in patients who fail to respond to monotherapy. Although specific combinations have rarely been evaluated, when using combination therapy, pharmacokinetic interactions with other AEDs need to be taken into consideration. In addition, there may be pharmacodynamic interactions. Adverse pharmacodynamic interactions seem to be more common when carbamazepine is combined with the related drug oxcarbazepine [51]. CNS-related adverse effects also frequently occur when carbamazepine is combined with lamotrigine, though this can be managed with a reduction of the carbamazepine dose [52].

Efficacy in non-epilepsy conditions

In many countries, carbamazepine's efficacy in trigeminal neuralgia was demonstrated even before the drug was licensed for epilepsy [53]. Carbamazepine remains a first-line treatment for this indication. Randomized controlled trials have also shown efficacy in other neuropathic painful disorders, such as diabethic neuropathy [54]. The efficacy of carbamazepine in the maintenance treatment of bipolar disorders has also been shown in randomized trials, where the drug seems most effective in preventing manic episodes [54].

Adverse effects

In clinical trials, approximately 10–25% of patients randomized to carbamazepine discontinued treatment because of adverse effects [31,33,34,38,55]. The frequency is even higher in some studies in the elderly [35,42]. Adverse effects are either idiosyncratic, most often a rash, or dose-related CNS effects. The frequency of CNS-related adverse effects depends on titration rate, target dosage as well as type of formulation [56]; in particular, CNS tolerability seems to be better with sustained-release than with immediate-release formulations [43]. Titration rate and target dosage also affect the risk of some idiosyncratic effects [57].

The prevalence of adverse effects declines with duration of treatment. CNS-related adverse effects such as sedation, cognitive disturbances, change in mood and diplopia, as well as gastrointestinal symptoms, were considerably less frequent after 12 months than early in treatment in a large Veterans' Affairs double-blind randomized study [32]. This has been attributed in part to autoinduction of carbamazepine metabolism resulting in a gradual decline in serum drug concentrations over the first few weeks. However, development of tolerance at pharmacodynamic level seems to be a more important determinant of the time-dependent reduction in adverse effects.

Carbamazepine is overall better tolerated than some other older generation AEDs, such as primidone and phenobarbital [31]. Data on differences in tolerability between carbamazepine and valproate are conflicting [32,39,44]. Carbamazepine has been the comparator in a large number of randomized controlled trials of newer generation AEDs in patients with newly diagnosed epilepsy. Most of these studies indicate a better tolerability, particularly lower rash rates, with the newer AEDs [33,35,37,38,41,42,55,58]. However, it has been suggested [56] that the use of suboptimal drug formulations, dosages and titration rates may have contributed to the apparent poorer tolerability of carbamazepine compared with lamotrigine [35,38,41,42] gabapentin [38,42,55], oxcarbazepine [37] and vigabatrin [55,58]. When sustained-release carbamazepine was used with a slow titration and with an adequately low target dosage in two double-blind randomized trials, overall tolerability was essen-

Table 36.5 Frequency (% of exposed patients) of different adverse events reported by patients treated with carbamazepine in two large randomized trials.

	Marson *et al.*, 2007 [38]	Brodie *et al.*, 2007 [34]
Number randomized	378	291
Adverse event		
Headache	3.7	25.4
Fatigue	12.7	14.1
Depression	3.7	2.1
Rash	10.1	5.5
Dizziness	3.7	13.7
Nausea	2.4	10.7
Weight gain	2.4	6.5

tially comparable to that observed with lamotrigine [43] and levetiracetam [34].

The most common adverse events reported by patients on carbamazepine in the two largest randomized monotherapy trials are listed in Table 36.5. The SANAD study [38] was a pragmatic unblinded long-term trial in which physicians could use either sustained-release or immediate-release carbamazepine, whereas the study by Brodie *et al.* [34] was a double-blind comparison between controlled-release carbamazepine and levetiracetam. These, and other differences between the two trials, may have contributed to the different frequencies of adverse events, which were mostly CNS related in both studies.

CNS effects

The most common adverse CNS effects of carbamazepine are dose related, occur mostly at the beginning of treatment and are reversible. Those most common include drowsiness, dizziness, asthenia, ataxia, diplopia and blurring of vision. Less common neurological adverse effects include dystonic movements, choreoathetosis and other dyskinesias and asterixis.

Psychic disturbances are relatively uncommon adverse effects of carbamazepine therapy, at least compared with other major AEDs. They include restlessness, insomnia, agitation, anxiety, mania and other psychoses.

At usual doses, carbamazepine appears to have little effect on cognitive function. The large randomized Veterans' Affairs study that compared carbamazepine with phenytoin, phenobarbital and primidone in 622 patients used an extensive battery of neuropsychological tests. In this comparison, patients on carbamazepine had the most favourable scores [59]. A follow-up Veterans' Affairs study that compared carbamazepine with valproic acid observed no differences in cognitive or behavioural scores between the two treatments and no deterioration in neuropsychological tests compared with pre-treatment [60]. In a study of seizure-free children, withdrawal of older generation AEDs, including carbamazepine, had very limited effects on cognitive function [61].

An open-label comparative trial reported improved cognitive functions on repeated testing in patients randomized to vigabatrin, whereas no change was seen in patients randomized to carbamazepine [58]. This was interpreted as lack of a practice effect on test performance in the carbamazepine group. Levetiracetam produced fewer adverse neuropsychological effects than carbamazepine in a randomized, double-blind, two-period cross-over design [62], but two more recent reports found no significant differences in overall adverse CNS effects between these drugs [34,63]. No significant differences in cognitive effects were found between tiagabine and carbamazepine used as monotherapy in newly diagnosed adults with partial epilepsy [64]. As discussed above, in randomized controlled trials tolerability (including adverse CNS effects) has been reported to be significantly poorer with carbamazepine than with lamotrigine [35,38,41,42], oxcarbazepine [37] and gabapentin [42,55]. This difference, however, could be partly related to study designs and suboptimal use of carbamazepine.

Cutaneous hypersensitivity reactions (including cutaneous reactions associated with systemic symptoms)

Skin rashes occur typically in 5–15% of patients started on carbamazepine, but in up to 19% of cases in the elderly [41]. Rash rates appear to be lower in children, being estimated at approximately 5% in paediatric epilepsy groups. The vast majority of these reactions are benign. They tend to occur within the first 8 weeks of treatment and disappear on drug withdrawal. There is a considerable cross-reactivity with some other AEDs such as phenytoin, phenobarbital, oxcarbazepine and probably also with lamotrigine. Between 30% and 60% of patients who experienced a rash on carbamazepine will have a recurrence if switched to any of these drugs [57,65]. Therefore, if possible, such drugs should be avoided in patients with previous skin reactions to carbamazepine.

Serious and even life-threatening hypersensitivity skin reactions can occur with carbamazepine, but these constitute only a very small proportion of all cutaneous reactions observed in patients treated with this drug. Drug-related rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) all belong to this category [57]. DRESS, also known as the anticonvulsant hypersensitivity syndrome, is characterized by fever, skin manifestations, eosinophilia, atypical lymphocytosis, lymphadenopathy, arthralgia and multiorgan involvement [57] and has been estimated to occur in 1.0–4.1 cases per 10 000 treated with carbamazepine [66]. SJS and TEN are characterized by bullous skin reactions combined with mucosal and sometimes also systemic involvement. Their incidence has been estimated at 0.5–2 per 10 000 carbamazepine exposures, which is comparable to risk estimates for lamotrigine, phenobarbital and phenytoin [66,67]. The risk of SJS appears to be higher in the Chinese Han ethnic group and in some other Asian groups than in whites, and recent research in Chinese patients has demonstrated a highly significant association between the presence of the HLA-B*-1502 allele of the human leucocyte antigen and a greatly increased risk of SJS and TEN [57,68,69]. Because the frequency of the HLA-B*-1502 allele is much greater in some Asian populations than in whites, the recommendation has been made that subjects belonging to these ethnic groups should undergo genotyping for HLA-B*-1502 before starting carbamazepine, and that carbamazepine should be preferably avoided in patients with this genotype. Like trivial skin rashes, severe hypersensitivity reactions associated with carbamazepine generally occur in the first 3 months of treatment. Any indication of such symptoms necessitates immedi-

ate withdrawal of the drug. Since it may be difficult to distinguish between early symptoms of severe hypersensitivity reactions and benign rashes, the occurrence of a rash during the first few months of carbamazepine treatment normally prompts withdrawal of the drug.

Desensitization by rechallenge with low and slowly increasing doses has been described to be successful in some patients with carbamazepine-associated rash, but this procedure is generally not recommended unless there has been a careful evaluation of the risk–benefit balance. In general, the risk of hypersensitivity reactions seems to be reduced if carbamazepine is introduced at a low dose and with a slow up-titration to the target maintenance dose. Rapid introduction of carbamazepine should therefore be avoided whenever the clinical situation permits.

Haematological adverse effects

Carbamazepine may induce a folate deficiency. This effect develops during chronic use, is possibly related to enzyme induction, and it is often associated with a modest macrocytosis. Frank megaloblastic anaemia is, however, rare.

Several cases of carbamazepine-induced blood dyscrasias have been reported. The incidence of aplastic anaemia has since been estimated at 0.5–2 per 100 000 patients exposed [57]. Agranulocytosis is also quite rare. In a population-based study, carbamazepine contributed to 5 out of 177 identified cases of agranulocytosis [70], with an odds ratio of 11.0 (1.2–102.6) compared with unexposed persons in the general population, in which the incidence is estimated to be 3.5 per million person-years.

Thrombocytopenia occurs in sporadic cases, whereas a clinically insignificant decrease in white cell counts under 4000–5000 cells/mm^3 is common and can be found in about one-third of carbamazepine-treated patients during the first 6 months of therapy. A leucopenia with decreasing number of cells needs consideration, but in most cases leucopenia is transient and very seldom prompts withdrawal of the treatment.

Because of the rarity of the serious haematological reactions and the questionable preventive effectiveness of blood cell counts, regular laboratory monitoring is generally not considered justified.

Hepatotoxicity

Carbamazepine may induce two types of clinically significant liver pathology. One is hypersensitivity-induced granulomatous hepatitis associated with cholestasis, and the other is a 'toxic-type' hepatitis without cholestasis. Acute hepatotoxicity is, in any case, rare. Its incidence has been estimated at 16 cases per 100 000 treatment years, based on data from a spontaneous adverse drug reaction reporting system [71]. It usually appears early, in most cases within 3–4 months after initiation of treatment.

In contrast to acute hepatotoxicity, a modest and benign elevation of liver enzymes is a common phenomenon, seen in 5–22% of patients on carbamazepine treatment. An increase in γ-glutamyltransferase is particularly frequent, and is regarded as an epiphenomenon of the induction of microsomal liver enzymes caused by carbamazepine. An isolated increase in γ-glutamyltransferase does not justify drug withdrawal. In most cases, modest elevations in aminotransferases are clinically insignificant.

Endocrinological effects

Antidiuretic hormone and hyponatraemia

Treatment with carbamazepine can result in hyponatraemia, although the risk is significantly lower than with oxcarbazepine. Hyponatraemia is in most cases modest and asymptomatic and does not require withdrawal of the drug or other actions [72]. It may, however, become occasionally severe and evolve to water intoxication, necessitating a restriction in water intake and a change in AED treatment. The risk of hyponatraemia increases with increasing carbamazepine dosage and with increasing serum carbamazepine concentration, and is generally more common in the elderly than in the young. The mechanism behind the hyponatraemic effect of carbamazepine is unclear. A drug-induced elevation in antidiuretic hormone levels, a sensitization of the renal tubules to the action of antidiuretic hormone, and other mechanisms have all been suggested.

In addition to causing a decrease in plasma sodium, carbamazepine may reduce the plasma concentrations of calcium and chloride.

Thyroid hormones

Carbamazepine is known to reduce the serum concentrations of thyroid hormones, particularly total and free thyroxine, whereas effects on serum triiodothyronine are more variable. These hormonal changes are usually of no clinical relevance [73,74]. However, a hypothyroid state may develop in patients with preexisting thyroid disease on thyroxine replacement therapy, since carbamazepine-associated enzyme induction results in accelerated catabolism of thyroid hormones and, consequently, increased thyroxine dosage requirements.

Sex hormones

Carbamazepine and enzyme-inducing AEDs can lower bioactive sex hormone concentrations, partly by decreasing their serum concentrations and partly by increasing serum sex hormone-binding globulin [75]. The net effect can be a diminished bioactivity of testosterone and estradiol. Effects on sex hormone concentrations appear to be reversible on withdrawal of treatment, even after years of carbamazepine use [76]. The clinical consequences of carbamazepine-induced changes in sex hormones could be diminished potency in men and menstrual disturbances in women. The frequency of these adverse effects is, however, uncertain (see Chapter 25 for a detailed discussion on reproductive function in people with epilepsy).

Bone metabolism

Some AEDs adversely affect bone mineralization, resulting in an increased risk of fractures. Enzyme-inducing AEDs, including carbamazepine, have been most commonly associated with alterations of biochemical parameters of bone turnover and with a decrease in serum 25-hydroxyvitamin D levels in cross-sectional studies [77]. Similar findings have, however, been reported also with valproate [77].

A recent prospective follow-up study of young women on monotherapy with carbamazepine, lamotrigine, phenytoin or valproate reported significant femoral bone loss over 1 year in

the phenytoin-treated women [78]. In contrast, those on carbamazepine, lamotrigine or valproate did not show detectable changes in bone turnover or bone mineral density. Further studies are needed to elucidate in more detail the effects of carbamazepine on bone metabolism and the potential consequences thereof.

Cardiac adverse effects

Carbamazepine may cause cardiac adverse effects, including bradycardia, Adams–Stokes attacks, aggravation of sick sinus syndrome, other conduction disturbances, tachyarrhythmias and development of congestive heart failure. Cardiac complications have been classified into two groups [79]. One group consisted exclusively of sinus tachycardia and was observed mostly in association with high serum carbamazepine levels, generally as a result of deliberate overdose. The other group consisted of potentially life-threatening bradyarrhythmias or atrioventricular conduction delay and was observed predominantly in older patients (more commonly in females), usually at serum carbamazepine concentrations within the reference range.

Overall, adverse cardiac effects in patients receiving therapeutic doses of carbamazepine are relatively uncommon, and probably occur mainly in susceptible individuals with pre-existing cardiac abnormalities [80]. Therefore, an electrocardiogram is recommended before initiation of carbamazepine treatment, particularly in the elderly.

Very rarely, the heart may be involved in systemic hypersensitivity reactions to carbamazepine, including eosinophilic myocarditis.

Teratogenic effects and postnatal development

Recent data from large-scale prospective registries suggest a rate of major congenital malformations of 2.2–3% in association with carbamazepine monotherapy [81]. This is lower than in earlier studies and not so greatly increased over the rate expected in the general population as previously thought. The prevalence of major malformations in the offspring of mothers treated with carbamazepine in monotherapy is lower than with valproic acid and comparable to that reported with lamotrigine [81].

In a case–control study based on 8005 cases of malformations in an international registry, 299 infants had been exposed *in utero* to carbamazepine [82]. Among these infants, the only significant malformations were hypertelorism and localized skull defects, spina bifida on monotherapy and cardiac malformations on polytherapy. Earlier reports have also indicated an increased risk of neural tube defects (absolute risk: 0.5–1%) after carbamazepine exposure [83]. This finding is important in guiding prenatal diagnostic tests.

Prospective population-based studies do not suggest any adverse effects on postnatal cognitive development in children exposed to carbamazepine *in utero* [84], although more data are needed.

Early studies suggested potential adverse effects of carbamazepine (and other AEDs) on intrauterine growth. Wide *et al*. [85], however, assessed body measures in infants exposed prenatally to AEDs in a Swedish population over a period of 25 years in comparison with data from the general population. There was a clear trend towards normalization of the head circumference over the time period considered, in parallel with a shift from polytherapy towards monotherapy, despite an increasing use of carbamazepine.

Miscellaneous adverse effects

Cholesterol metabolism may be affected by carbamazepine in both children and adults, leading to elevations in high-density lipoprotein (HDL) cholesterol concentrations and HDL to total cholesterol ratio.

Renal effects are rare and include proteinuria, haematuria, oliguria and renal failure. Acute renal failure has been described in a few patients on carbamazepine treatment, and attributed to acute interstitial nephritis, acute tubular necrosis or membranous glomerulopathy. Few patients have also had interstitial nephritis and exfoliative dermatitis, nephrotic syndrome or a combination of nephropathy, haemolytic anaemia and thrombocytopenia.

Like other enzyme-inducing AEDs, exposure to carbamazepine *in utero* has been associated with vitamin K deficiency in the newborn.

Adverse effects and quality of life studies

Gillham *et al*. [86] compared the impact of carbamazepine and lamotrigine on health-related quality of life using a modified Side Effect and Life Satisfaction (SEALS) inventory divided into five subscales: worry, temper, cognition, dysphoria and tiredness. A total of 260 patients with newly diagnosed epilepsy were randomized to 48 weeks of treatment with carbamazepine or lamotrigine. The only significant difference, which was in favour of lamotrigine, was at week 4. This is in line with previous experiences with carbamazepine suggesting that tolerability improves after the first weeks of treatment and is comparable to that of other major AEDs during long-term therapy.

The randomized unblinded SANAD trial included quality-of-life measures in its comparisons of carbamazepine, lamotrigine, gabapentin and topiramate in adults with newly diagnosed partial epilepsy [38]. This large study found no important differences or trends for scores between these treatments on the Adverse Events Profile, the Neurotoxicity Scale, the EQ-5D scale or for global quality of life.

Massive overdose and intoxication

In adults on carbamazepine treatment, the lowest known lethal dose has been estimated at approximately 60 g. A 6-year-old child survived 10 g and a 3-year-old child survived 5 g. The maximum tolerable dose varies within wide limits and depends on the time elapsed since ingestion. Several hundred patients with massive overdoses, fatalities included, have been reported.

In adults, carbamazepine concentrations of ≥40 μg/mL (≥170 μmol/L) have been significantly associated with serious dysfunctions of several organ systems, including cardiac conduction disorders, respiratory failure, seizures and coma.

Four clinical stages of carbamazepine intoxication have been described [87]: (a) coma and seizures [serum concentrations >25 μg/mL (106 μmol/L)]; (b) moderate stupor, combativeness, hallucinations, choreiform movements [15–25 μg/mL (64–106 μmol/L)]; (c) mild drowsiness, ataxia [11–15 μg/mL (46–64 μmol/L)]; and (d) possibly mild ataxia, but otherwise normal neurological examination [<11 μg/mL (<46 μmol/L)]. Sudden and potentially catastrophic relapse to stages (a) to (c) may occur unexpectedly during stage (d).

Determinations of serum drug concentrations are important in predicting the severity of intoxication. In children, however, the serum concentration of carbamazepine may not predict accurately the severity of toxic manifestations. In children, the carbamazepine half-life may be prolonged and the carbamazepine-10,11-epoxide concentration is increased, sometimes at levels even higher than the concentration of the parent drug.

In addition to symptomatic therapy, carbamazepine intoxication may be managed with repeated gastric lavage and haemoperfusion. Forced diuresis, cathartics, peritoneal dialysis, plasmapheresis and haemodialysis should be avoided. Seizures should be treated with benzodiazepines.

Place in current therapy

Carbamazepine is a first-line AED for the treatment of children and adults with partial-onset seizures, with or without secondary generalization. Given that no other drug has been shown to be more effective, and in view of its usually good tolerability, carbamazepine can be considered as the drug of first choice for this patient population. Other treatment alternatives could be considered as first choice in the elderly, in whom carbamazepine appears to be less well tolerated, and in patients on other medications, in whom the high interaction potential of carbamazepine could complicate clinical management. Carbamazepine is also effective against generalized tonic–clonic seizures, and it could be regarded as one of the possible first-line drugs for this indication. However, other drugs are often preferred in patients with idiopathic generalized epilepsies, because carbamazepine lacks efficacy against absence and myoclonic seizures and may even precipitate or aggravate these seizure types.

Carbamazepine remains a first-line treatment for trigeminal neuralgia, and is also useful in other neuropathic pain syndromes. It may also be useful as a mood stabilizer in patients with bipolar disorder.

Dose and titration rates

Carbamazepine is commercially available as immediate-release and sustained-release tablets, as a suspension and as suppositories. However, no formulations are available for parenteral use. Sustained-release formulations are usually preferred to improve tolerability and can generally be used on a twice-daily regimen. With immediate-release formulations, patients receiving relatively high doses and patients with a fast metabolism of carbamazepine (e.g. children and patients co-medicated with enzyme-inducing AEDs) benefit from dividing the daily dose into three or even four administrations per day. This aids in preventing excessive fluctuations in serum drug concentrations and in avoiding high peak concentrations associated with adverse effects.

A slow and gradual titration to the initial target maintenance dose is important to reduce the risk of adverse effects. In children, treatment is often initiated with a daily dosage of no more than 5 mg/kg body weight, which is gradually increased over 2–4 weeks to an initial target maintenance dose of 10–20 mg/kg body weight per day. Adults are usually started on 100–200 mg/day, to be increased to an initial target maintenance dosage of approximately 400 mg/day over 2–4 weeks [88]. Dosage is subsequently adjusted based on clinical response, in accordance with the general principles of AED treatment.

In general, maintenance dosages after dose optimization are in the order of 5–30 mg/kg/day in children, while infants usually require higher dosages (10–40 mg/kg/day). The majority of adults with newly diagnosed epilepsy who respond to carbamazepine monotherapy do so at low dosages (400–600 mg/day). Optimal maintenance dosages in individual patients may range from 400 to 1600 mg/day and higher doses (up to 2400 mg/day) may be needed in difficult-to-treat patients co-medicated with enzyme-inducing AEDs. When carbamazepine is combined with other drugs, dosage may need to be adjusted to compensate for pharmacodynamic as well as pharmacokinetic interactions. In the case of pharmacokinetic interactions, dose adjustment is facilitated by monitoring serum carbamazepine concentrations.

Laboratory monitoring

It is advisable to take a blood sample for a complete blood count, determination of liver enzymes and serum electrolytes before starting treatment with carbamazepine, as with any other AED. The value of continued regular haematology and blood chemistry tests to identify rare idiosyncratic adverse effects is questionable, and repeated tests are not generally justified unless there are clinical signs or symptoms requiring special investigation. However, it is reasonable to repeat the initial laboratory check at a scheduled visit 2–4 months after initiation of treatment. The need for subsequent testing will depend on the clinical evolution. A routine electrocardiogram is also justified before starting carbamazepine to identify those few patients who may be at risk for cardiac adverse effects and to obtain a baseline for future comparison.

Therapeutic monitoring of serum carbamazepine concentrations is well established. A reference range of 4–12 μg/mL (17–51 μmol/L) has been suggested. Strict adherence to reference ranges, however, is not advisable because the optimal therapeutic concentration varies across individuals in relation to a wide variety of factors [29]. Carbamazepine dosage is best adjusted according to clinical response rather than to a predefined range of serum concentrations. However, it is useful to establish empirically the optimal serum concentration of the drug in individual patients. This is ideally done by determining the trough (before morning dose) carbamazepine concentration at steady state on the patient's maintenance dose. A further sample is drawn under the same conditions if the dosage is increased due to unsatisfactory seizure control. Once the individual optimal (therapeutic) concentration has been determined, this can serve as a useful reference to determine whether subsequent possible changes in clinical response are related to an alteration in serum drug levels. Based on these considerations, a case can be made for measuring the serum carbamazepine concentration a few weeks after the patient has reached the target dose, when the optimal dose has been established, when seizure control is poor or deteriorated (also as a check for compliance), when dose-related adverse effects are suspected, or when drug–drug interactions or other conditions are anticipated which can affect the pharmacokinetics of carbamazepine. In general, there is little value in measuring the unbound serum carbamazepine concentration, and the total

concentration is sufficient. Routine determination of the active metabolite carbamazepine-10,11-epoxide metabolite is usually not justified.

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37 Carisbamate

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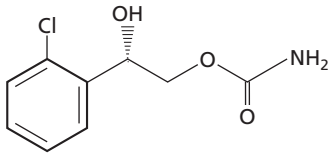

Primary indications	Adjunctive therapy of refractory partial-onset seizures with or without secondary generalization (potential additional indications are being considered)
Usual preparation	Tablets: 100 mg, 200 mg and 400 mg
Usual dosages	300–800 mg/day (tentative)
Dosing frequency	Twice daily
Significant drug interactions	Antiepileptic drugs which induce uridine glucuronosyltransferase (UGT) decrease plasma carisbamate concentrations by stimulating its metabolism. Plasma carisbamate concentrations may be moderately decreased by steroid oral contraceptives. Carisbamate causes a modest decrease in the plasma concentrations of lamotrigine and a moderate increase in the plasma levels of tolbutamide
Serum level monitoring	There is insufficient information on the value of monitoring serum carisbamate levels
Reference range	Not clearly defined
Common/important adverse effects	Headache, diplopia, vertigo, dizziness, somnolence, nausea, vomiting, gait disturbance, abnormal coordination
Main advantages	Good tolerability at dosages at least up to 800 mg/day
Main disadvantages	Modest responder rates in trials conducted to date, possibly due to doses lower than optimal. Metabolism susceptible to enzyme induction
Mechanism of action	Blockade of voltage-gated sodium channels. Additional mechanisms are likely
Oral bioavailability	≥90%
Time to peak levels	0.5–3 h fasting (2.5–5 h when taken with food)
Elimination	Primarily by metabolism, including glucuronide conjugation and hydrolysis of the carbamate ester followed by oxidation
Apparent volume of distribution (V_d/F)	Approximately 50 L
Elimination of half-life	10–13 h (may be shorter in patients co-medicated with UGT-inducing drugs)
Apparent plasma clearance (CL/*F*)	3.4–4.2 L/h (may be higher in patients co-medicated with UGT-inducing drugs)
Protein binding	47%
Active metabolites	None known
Comment	Potentially a useful antiepileptic drug, but more data are needed to establish the optimal dose range and its place in current therapy

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Introduction

Carisbamate (*S*-2-*O*-carbamoyl-1-*o*-chlorophenyl-ethanol) is a novel agent under development for the treatment of epilepsy. Carisbamate displayed a favourable profile in preclinical models of epilepsy, demonstrating broad-spectrum anticonvulsant activity. It was shown subsequently to possess efficacy and tolerability in a phase II clinical trial, and two phase III clinical trials have recently been completed. This chapter will review the preclinical data, pharmacokinetics, efficacy, safety and tolerability of this compound.

Chemistry

Carisbamate is a white to off-white powder that is freely soluble in propylene glycol and ethanol and has limited water solubility. The molecular formula of carisbamate is $C_9H_{10}ClNO_3$, and its molecular structure is depicted in the summary table on the opening page of this chapter. The chiral centre of the molecule is carbon 1, and carisbamate comprises the S-enantiomer. The molecular weight of carisbamate is 215.63; its melting point is 132–136°C.

Pharmacology

Activity in experimental models of seizures and epilepsy

The antiepileptic activity of carisbamate was assessed in a battery of well-characterized rodent seizure models (including models of therapy-resistant seizures and epilepsy). Results obtained from these studies confirm that it possesses a high potency and a favourable therapeutic index, and suggest a broad spectrum of activity against a variety of seizure types, including generalized tonic–clonic seizures, complex partial seizures, generalized absence seizures and myoclonic seizures [1–3].

In mice, carisbamate exhibited potent activity in the maximal electroshock (MES), pentylenetetrazol, bicuculline and picrotoxin seizure models. Carisbamate was also active in the MES model in rats (Table 37.1) [1]. The median effective dose (ED_{50}) values for oral administration in the MES test were 7.7 mg/kg in mice and 4.4 mg/kg in rats [1]. In mice, carisbamate significantly elevated the threshold for intravenous pentylenetetrazol-induced seizures when tested at a dose high enough to produce motor impairment [1]. The results from the intravenous pentylenetetrazol and MES tests suggest that carisbamate has the ability to control seizures by both elevating seizure threshold

Table 37.1 Carisbamate displays a broad-spectrum anticonvulsant profile in mouse and rat seizure models.

Species, route	Test	Time of test (h)	ED_{50} (mg/kg)	95% CI	Protective index[a]
Mice, i.p.	Rotorod	0.25	46.4[b]	35.9–65.6	
	Frings audiogenic seizures	0.25	4.25	3.51–6.95	11[c]
	MES	0.25	7.91	6.01–9.63	5.9
	Pentylenetetrazol s.c.[d]	0.25	20.4	11.5–29.6	2.3
	Bicuculline s.c.[d]	0.25	Max 5/8 protected at 17		
	Picrotoxin s.c.	0.25	11.6	8.40–14.5	4.0
Mice, p.o.	Rotorod	0.25	137[b]	112–174	
	MES	0.25	7.67	5.27–9.71	18
	Pentylenetetrazol s.c.	0.25	57.7	34.1–87.9	2.4
Rats, p.o.	Minimal motor impairment	1	139[b]	95.0–209	
	MES	1	4.39	2.87–6.44	32
	MES	5	8.08	6.50–9.79	17
	Pentylenetetrazol s.c.	1	>250		<0.6
	Corneal kindling	1	4.2	1–10	33
Rats, i.p.	Minimal motor impairment	0.25	39.5	36.9–42.4	
	Hippocampal kindling	0.25	22.5	12.5–37.5	1.8
	Li^+–pilocarpine status epilepticus	1	52.9	47.8–58.5	0.75
Rats, i.v.	Sustained Li^+–pilocarpine status epilepticus		20 and 30 mg/kg	Immediate but transient termination of status in 4/5 rats[e]	

From ref. 1 with permission.

CI, confidence interval; ED_{50}, median effective dose; i.p., intraperitoneal; i.v., intravenous; MES, maximal electroshock; p.o., oral; s.c., subcutaneous; TD_{50}, median toxic dose.

[a] Protective index = TD_{50}/ED_{50}.

[b] Median toxic dose (TD_{50}).

[c] Protective index was calculated with TD_{50} obtained in CF#1 mice and ED_{50} in Frings mice.

[d] In addition to blocking the clonic seizures, carisbamate also blocks tonic extension induced by s.c. pentylenetetrazol and s.c. picrotoxin; ED_{50} (95% CI): 14.3 (8.78–23.4) and 5.48 (3.67–8.19) mg/kg.

[e] Complete suppression of status epilepticus for at least 90 minutes in two of five rats at 30 mg/kg; in the remaining rats, seizures resumed at a lower severity (stage 3).

and preventing seizure spread. Moreover, the results from the intravenous pentylenetetrazol seizure threshold and Genetic Absence Epileptic Rat of Strasbourg (GAERS, see below) study suggest that carisbamate does not lower seizure threshold. Carisbamate also reduced seizure severity in the corneal-kindled rat model of partial epilepsy, and reduced seizure severity and afterdischarge duration in the hippocampal-kindled rat model.

In contrast to carbamazepine, phenytoin, lamotrigine and topiramate, carisbamate was effective in both the lamotrigine-resistant amygdala-kindled rat, and the 6-Hz seizure model, two models that are thought to have predictive value for pharmacoresistant epilepsy [1]. In the 6-Hz seizure model, carisbamate retained potent anticonvulsant activity as the stimulus intensity was increased from 22 to 44 mA [1]. In the lamotrigine-resistant amygdala-kindled rat, carisbamate caused a dose-dependent reduction in behavioural seizure score and afterdischarge duration. Carisbamate has also been demonstrated to delay the development of amygdala kindling when administered prior to each kindling stimulation during the kindling acquisition phase [4]. These results suggest that carisbamate might have disease-modifying effects in this model. In addition, carisbamate is effective in treating fully kindled rats, even when the animal has been kindled in the presence of carisbamate. In contrast, rats kindled in the presence of low-dose lamotrigine are resistant to a higher dose of lamotrigine [4].

Carisbamate has been evaluated in two genetic models of epilepsy, the GAERS and the Wistar Audiogenic Sensitive (AS) rat. In the GAERS, which is a model predictive of activity in absence seizures, carisbamate administered intraperitoneally (i.p.) at doses of 10, 30 and 60 mg/kg dose-dependently reduced the expression of spike-and-wave discharges as measured by electroencephalography; spike-and-wave discharges were significantly suppressed at 30 mg/kg and completely suppressed at 60 mg/kg [5]. In Wistar AS rats, carisbamate given i.p. significantly delayed seizure onset at 10 mg/kg and completely suppressed seizure-related behaviours at 20 and 30 mg/kg [5].

When administered i.p. in rats, carisbamate prevented the onset of lithium–pilocarpine-induced status epilepticus. Following intravenous administration, carisbamate interrupted fully established lithium–pilocarpine-induced status epilepticus (Table 37.1) [1]. In a hippocampal neuronal model of status epilepticus, carisbamate (100 μmol) significantly decreased depolarization-induced sustained repetitive firing. Carisbamate did not block low-Mg^{+}-induced high-frequency spiking in this model. However, this latter form of *in vitro* status epilepticus is not effectively blocked by conventional AEDs that are known to be effective in treating status epilepticus in humans [6]. Carisbamate performed well in suppressing spontaneous motor seizures in the kainate post-status epilepticus rat model of temporal lobe epilepsy. When administered at 10 or 30 mg/kg i.p. in this model, carisbamate significantly reduced relative seizure frequency (74% reduction at 30 mg/kg, $P < 0.0001$) [3] and was more effective than topiramate; that is, spontaneous seizures were completely suppressed by carisbamate in a larger fraction of the rats studied (seven of eight rats at 30 mg/kg i.p. for carisbamate versus one of eight rats at 100 mg/kg i.p. for topiramate) [2].

In the lithium–pilocarpine model of post-status epilepticus-induced epileptogenesis in male Sprague–Dawley rats, carisbamate displayed both neuroprotective and antiepileptogenic effects. When carisbamate (30, 60, 90 or 120 mg/kg) was injected i.p. at 1 and 8 h after the onset of lithium–pilocarpine-induced status epilepticus and the administration was continued twice daily for 6 days, the drug at all doses reduced neuronal loss, preserving neurones in the CA1 region of the hippocampus, the dorsolateral region of the lateral thalamus and the basolateral amygdala [7]. At 60 mg/kg, significant neuroprotection was also observed in the anterior part of the amygdala and layer II of the piriform cortex, and at 90 and 120 mg/kg, carisbamate further afforded marked neuroprotection in the posterior part of the medial amygdala, the ventrolateral part of the lateral thalamus, the mediodorsal thalamus and deep layers of the piriform, and ventral entorhinal cortices [7]. More importantly, carisbamate dose-dependently delayed or prevented the development of spontaneous recurrent seizures. At the higher doses of 90 and 120 mg/kg, 45% of the rats did not develop spontaneous recurrent seizures by the end of the 5-month-long study [7].

Studies in models predictive of activity in other indications

In addition to the investigations in seizure models, carisbamate has been assessed for its efficacy in a model of neuropathic pain. A study by White *et al*. [8] demonstrated that carisbamate prevents the development of mechanical allodynia produced by amygdala kindling in rats. The mechanism by which carisbamate attenuates mechanical allodynia has yet to be determined, but it is likely that carisbamate modulates the pathways involved in the central and/or peripheral sensitization of the nervous system following amygdala kindling. This finding suggests that carisbamate may be effective for the treatment of neuropathic pain [8].

Mechanisms of action

The precise mechanisms of action of carisbamate remain under investigation. Carisbamate was found to inhibit voltage-dependent brain-type sodium channels in a concentration- and state-dependent manner [9]. However, this mechanism of action probably does not explain the broad spectrum of activity that carisbamate possesses in preclinical seizure models. Therefore, additional work is necessary to further elucidate the actions of carisbamate at molecular level.

Non-clinical toxicology

Carisbamate has demonstrated efficacy in rodent seizure models at doses well below those that produce central nervous system (CNS) toxicity. The neurotoxicity of carisbamate has been evaluated by the rotorod and inclined-screen tests in mice, and by observed minimal motor impairment in rats. The single-dose oral median toxic dose (TD_{50}) was ≥137 mg/kg, resulting in a protective index (the ratio of TD_{50}/ED_{50}) of ≥17 (the median ED_{50} in the MES test was 7.7 mg/kg for mice and 4.4 mg/kg for rats). The intravenous maximum tolerated single dose in mice and rats was in the range of 360–600 mg/kg; these doses resulted in decreased activity, ataxia, sedation and prostration [10].

Repeated-dose oral toxicity studies were carried out in adult rats (up to 6 months) and in adult dogs (up to 12 months). No significant organ toxicity occurred even at exposures that were two- to three-fold greater than anticipated human therapeutic exposures. Toxicity was also evaluated in juvenile rats administered carisbamate orally from postnatal day 12 to 54. Adverse CNS effects were elicited only at doses of 80 mg/kg and 160 mg/kg, and carisbamate had no effect on learning, memory or reproductive function [10].

Carisbamate tested negative for genetic toxicity in the bacterial reverse mutation test, the *in vitro* human lymphocyte chromosomal aberration assay and the *in vivo* oral mouse bone marrow assay [10].

Pharmacokinetics

Overview of pharmacokinetic properties

Carisbamate is rapidly absorbed following oral administration. Maximum plasma concentrations are observed 0.5–3 h after single-dose administration under fasted conditions. Data on absolute bioavailability have not been obtained since an intravenous formulation for use in humans is not available. However, absorption must be nearly complete because an average of 93.8% or more of radioactivity was recovered in the urine following single-dose oral administration of a radiolabelled dose of carisbamate to eight healthy male subjects [11].

Food intake has minimal impact on the extent to which carisbamate is absorbed, as assessed by the area under the plasma concentration versus time curve (AUC). A delay in the mean time of maximum concentration (t_{max}) values of approximately 2 h and a decrease in the mean maximum plasma concentrations (C_{max}) of carisbamate by approximately 20% was seen when carisbamate was given in a fed state (Johnson and Johnson, data on file).

The apparent volume of distribution (V_d/F; ~45–56 L) of carisbamate is close to total volume of body water, indicating that the drug does not distribute extensively to tissues. The distribution of carisbamate between whole blood and plasma was close to unity, consistent with the previous observation of low to moderate protein binding of carisbamate in humans. Data from *in vitro* studies indicate that carisbamate is approximately 47% bound to human plasma proteins, independent of the total concentrations (Johnson and Johnson, data on file).

The majority of carisbamate is eliminated by two major metabolic pathways: O-glucuronidation of either the *S*-enantiomer (44% of the dose) or the *R*-enantiomer produced through chiral inversion (11% of the dose), and hydrolysis of the carbamate ester followed by oxidation (36% of the dose). Only a fraction of carisbamate undergoes hydroxylation on the benzene ring followed by sulphate conjugation (5% of the dose) [11]. Trace amounts of two premercapturic acid conjugates of carisbamate (<0.3% of the dose) were observed in the urine [11]. Carisbamate and its metabolites are excreted primarily in the urine (~94 ± 7% of the dose) with a small percentage excreted in the faeces (~2.5 ± 2% of the dose). Only about 2.4% of the total radioactivity recovered in the urine was unchanged drug in the radiolabelled study previously mentioned. The fraction of unchanged drug in the faeces was not determined. Total recovery in both urine and faeces was approximately 96% within 120 h after dosing [11].

Carisbamate has been demonstrated to have linear pharmacokinetics. Dose proportionality was evident after single doses ranging from 100 to 1500 mg and after twice-daily administration of 100–750 mg given as a capsule formulation to healthy subjects. The half-life of carisbamate in subjects not taking enzyme inducers was determined to be between 10.6 and 12.8 h, allowing for twice-daily dosing. Steady-state conditions are typically achieved within 3 days. The apparent oral clearance (CL/*F*) in healthy subjects is 3.4–4.2 L/h, which is less than 5% of liver blood flow and indicative of a low hepatic first-pass effect. Renal clearance was determined to be 0.042–0.094 L/h, confirming that carisbamate is eliminated primarily by metabolism. Because the pharmacokinetics of carisbamate has been shown to be consistent after single and repeat administration, it may be concluded that carisbamate does not induce or inhibit its own metabolism [2,12].

Pharmacokinetics in special groups

Elderly subjects

The pharmacokinetics of carisbamate were evaluated after twice-daily administration of 100 mg, 250 mg and 500 mg to the following three groups, each of which consisted of six healthy subjects: (1) medically stable elderly adults aged 65–74 years; (2) medically stable elderly adults aged ≥75 years; and (3) non-elderly healthy adults aged 18–55 years. Small and clinically insignificant differences in the mean C_{max} and $AUC_{12\,h}$ values were observed [13].

Renal disease

When the pharmacokinetics of a single 200-mg dose of carisbamate was evaluated in patients with renal dysfunction, only clinically insignificant differences were observed in the mean plasma C_{max} and $AUC_{0–48h}$ values of unchanged carisbamate for subjects with moderate (creatinine clearance, 30–50 mL/min) to severe (creatinine clearance, <30 mL/min) renal impairment compared with subjects with normal renal function. However, the mean C_{max} and $AUC_{0–48h}$ of two glucuronide metabolites of carisbamate were up to 7.5 times higher in subjects with moderate and severe renal impairment and up to 50 times higher in subjects with end-stage renal disease (ESRD) relative to healthy subjects. A 4-h haemodialysis session reduced the AUC and C_{max} of the glucuronide metabolites by approximately 50% in subjects with ESRD, showing that they are effectively cleared from the plasma through dialysis (Johnson and Johnson, data on file).

Hepatic disease

The pharmacokinetics of carisbamate was evaluated in subjects with mild and moderate hepatic impairment and compared with the pharmacokinetics in subjects with normal hepatic function (10 subjects in each cohort). Following a single 200-mg dose of carisbamate, mean systemic exposure (plasma AUC) of carisbamate was approximately 16% greater

in subjects with mild hepatic impairment (Child–Pugh score 5–6) and 107% greater in subjects with moderate hepatic impairment (Child–Pugh score 7–9) compared with subjects with normal hepatic function. Furthermore, the pharmacokinetic profile of carisbamate in subjects with moderately impaired liver function was characterized by a prolongation in the mean terminal half-life (20.7 h) when compared with healthy subjects (10.5 h) [14].

Drug interactions

Studies *in vitro*

In human liver microsomes, carisbamate, at concentrations well above the maximal human exposure, inhibited CYP3A4 (IC_{50} = 695 μg/mL) and CYP2C9 (IC_{50} > 1000 μg/mL). In cultured primary human hepatocytes, carisbamate at 200 μg/mL (approximately 5–7 times the maximal human exposure) modestly induced CYP2B6 and CYP3A4/5 (activity increased 6.7 and 7.8 times, respectively). CYP2C9 was inhibited as well (activity decreased by 60%). Thus, carisbamate showed little propensity to interact with CYP at clinically relevant concentrations (Johnson and Johnson, data on file).

Studies *in vivo*

Three studies evaluating potential interactions with carbamazepine [15], lamotrigine [16] and valproic acid [16] were conducted and involved the following sequential treatments: (1) carisbamate monotherapy for 10 days (500–1000 mg/day); (2) monotherapy with the other antiepileptic drug (AED) for 11–28 days; and (3) concomitant administration of the two drugs for 10–17 days. Mean carisbamate exposure was reduced by approximately 40% and the terminal half-life was reduced from 10.4 h to 7.4 h by the co-administration of carbamazepine (600 mg/day), but carisbamate (1000 mg/day) did not affect the pharmacokinetics of carbamazepine. Lamotrigine (100 mg/day) had no significant effect on carisbamate pharmacokinetics, but the mean 12-h AUC value of lamotrigine was reduced approximately 22% by carisbamate (1000 mg/day). There was no significant interaction between valproic acid (1000 mg/day) and carisbamate (1000 mg/day); exposures of both drugs were well within the bioequivalency range (80–125%).

The potential interaction of carisbamate with other drugs has also been studied. When carisbamate (400 mg/day) was administered for 2 weeks to patients with epilepsy taking a wide range of phenytoin doses regimens, the mean steady-state plasma AUC values of carisbamate were up to 52% lower relative to the values in subjects who received carisbamate alone (Johnson and Johnson, data on file). This interaction was unidirectional and carisbamate did not alter the steady-state plasma concentrations of phenytoin. Carisbamate (400 mg/day, administered for 2 weeks) has been shown to have no effect on the pharmacokinetics or pharmacodynamics of a single dose of warfarin or ethanol (Johnson and Johnson, data on file).

There are some data to suggest that oral contraceptives lower carisbamate exposure: in one study, the mean steady-state AUC of carisbamate (1000 mg/day for 10 days) was reduced by 20–30% with concomitant administration in three consecutive cycles of an oral contraceptive containing 0.035 mg ethinylestradiol and 1 mg norethindrone (Johnson and Johnson, data on file). However, in another study the exposure of carisbamate (400 mg/day for 2 weeks) was reduced only 14% by an oral contraceptive containing 0.025 mg ethinylestradiol and 0.18–0.25 mg norgestimate (Johnson and Johnson, data on file). Carisbamate at dosages of 1000 mg/day reduced exposures of ethinylestradiol by no more than 13%, and norethindrone by no more than 5%; thus, impairment of contraceptive efficacy by carisbamate is unlikely.

Three *in vivo* studies evaluating the potential of carisbamate to affect the activity of cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2D6, using the probe substrates midazolam, tolbutamide and desipramine, respectively, involved the following sequential treatments: (1) a single dose of the enzyme probe drug; (2) carisbamate monotherapy (500–1000 mg/day) for 9 days; and (3) a single dose of the probe drug given concomitantly with carisbamate on day 9. The results indicated that carisbamate may be a weak CYP2C9 inhibitor, as this regimen increased the AUC_{∞} of tolbutamide by 31%. This regimen of carisbamate had little effect, however, on desipramine and midazolam, suggesting that carisbamate does not significantly affect CYP2D6- or CYP3A4-mediated metabolism (Johnson and Johnson, data on file).

Serum level monitoring

At present, there is insufficient information on the potential value of monitoring serum carisbamate levels.

Efficacy

Proof of-concept photosensitivity study

The initial clinical data on carisbamate's efficacy came from a multicentre, non-randomized, single-blind, placebo-controlled, proof-of-concept study that assessed the effect of carisbamate on the photoparoxysmal response to intermittent photic stimulation in 18 patients with photosensitive epilepsy [17]. The patients, all of whom were on a regimen of concomitant AEDs such as valproic acid, underwent standardized intermittent photic stimulation under three eye conditions (during eye closure, eyes closed and eyes open) each hour for up to 8 h on three consecutive days, after receiving placebo on day 1, carisbamate on day 2 and placebo on day 3. Doses of carisbamate on day 2 ranged from 250 to 1000 mg, and photosensitivity was evaluated at frequencies from 2 to 60 Hz. A dose-dependent reduction in photosensitivity was produced in the 13 evaluable patients (four patients each at the 500-mg and 750-mg dose level and five patients at the 1000-mg dose level): three patients (one in the 500-mg group and two in the 1000-mg group) exhibited complete suppression, and seven additional patients exhibited clinically significant suppression. All five patients in the 1000-mg group demonstrated reduction or complete suppression of the photoparoxysmal response. The onset of effect of carisbamate was rapid (occurring within 2 h of the time the dose was given for the 1000-mg dose), and the duration of effect was dose dependent and long lasting (clinically significant reductions of photosensitivity were observed for up to 32 h after doses of 750 or 1000 mg).

Randomized controlled trials in patients with partial-onset seizures

The efficacy and safety of carisbamate as adjunctive treatment of adults with partial-onset seizures has been assessed in three multicentre, randomized, double-blind, placebo-controlled studies.

Study 1 evaluated the safety and efficacy of daily dosages of 100, 300, 800 and 1600 mg of carisbamate added to up to three concomitant AEDs in patients with partial-onset seizures from 18 to 70 years in age ($n = 537$). These patients had a median duration of epilepsy of 22 years and had previously been exposed to a median of six different AEDs; 17% had been exposed to more than 10 AEDs and, overall, 36% of patients were receiving three concomitant AEDs. To be eligible for randomization, all patients had to have at least three partial-onset seizures per 28-day period during a prospective 8-week baseline period; the median was 10 per 28 days across all treatment groups (range, 3–445 per 28 days). The 16-week double-blind treatment phase included a 4-week titration phase. An intention-to-treat analysis was conducted for the primary outcome variable (per cent reduction in partial-onset seizure rate during the 16-week double-blind treatment phase relative to the 8-week prospective baseline phase) and each of the carisbamate doses was compared with the placebo using a Wilcoxon rank sum test stratified by pooled centres, with adjustment for multiplicity using a stepwise procedure. The 300 mg/day, 800 mg/day and 1600 mg/day doses were significantly more effective than placebo in reducing the frequency of partial-onset seizures (Fig. 37.1). The difference from placebo was evident for each of these dose groups within the first month of treatment and was maintained until the end of the double-blind period. For the responder rate (proportion of patients having a ≥50% reduction from baseline in partial-onset seizure frequency), each of the carisbamate doses was compared with placebo using the generalized Cochrane–Mantel–Haenszel test controlling for pooled analysis centre, with adjustment for multiplicity using a stepwise procedure. Carisbamate doses of 300 mg/day and 1600 mg/day were also associated with statistically significant overall responder rates (Fig. 37.2) [18].

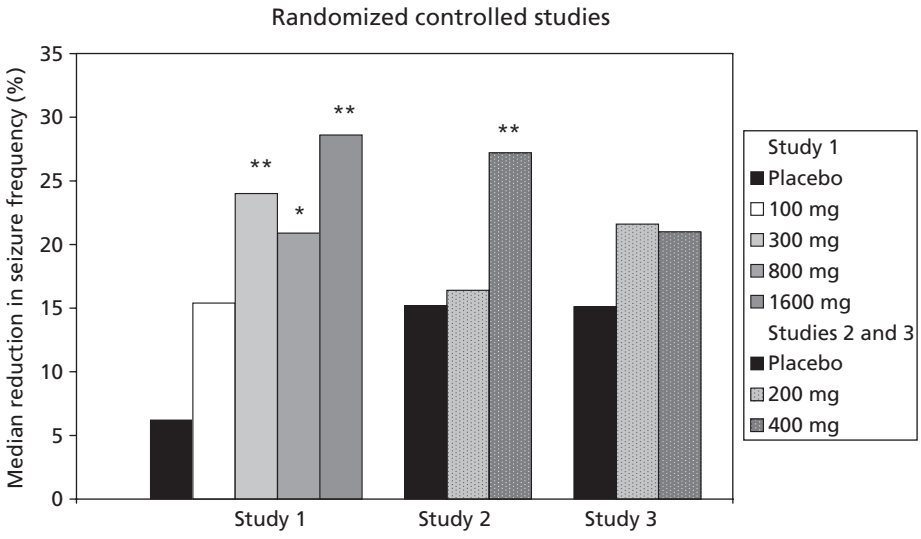

Fig. 37.1 Median per cent reduction in the frequency of partial-onset seizures from baseline in three randomized parallel-group placebo-controlled adjunctive therapy studies of carisbamate in patients with refractory partial epilepsy. *P*-values refer to comparisons with the placebo group. *$0.01 < P < 0.001$; **$P < 0.001$.

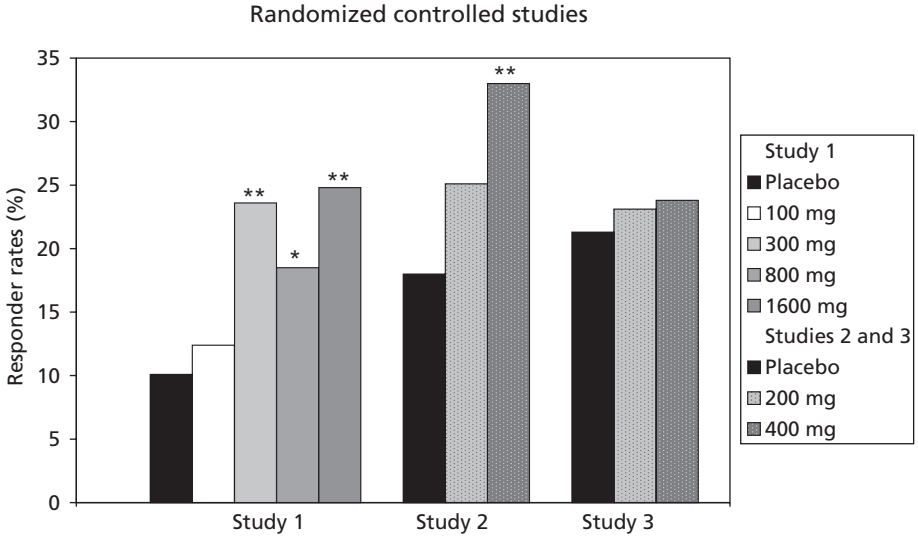

Fig. 37.2 Responder rates (percentage of patients with at least 50% reduction in the frequency of partial-onset seizures from baseline) in three randomized parallel-group placebo-controlled adjunctive therapy studies of carisbamate in patients with refractory partial epilepsy. *P*-values refer to comparisons with the placebo group. *$0.1 < P < 0.05$; **$0.01 < P < 0.001$.

Table 37.2 Per cent reduction from baseline in partial-onset seizure frequency by treatment group in relation to enzyme induction status in three randomized parallel-group placebo-controlled adjunctive therapy studies of carisbamate in patients with refractory partial epilepsy (intent-to-treat analysis set).

Treatment group and daily dose		Study 1		Study 2		Study 3	
		I	NI	I	NI	I	NI
Placebo	*n*	62	47	94	89	117	71
	Median	12.2	3.8	14.1	16.1	15.2	15.0
	Range	–151 to 86	–277 to 100	–1300 to 100	–229 to 90	–258 to 100	–308 to 100
Carisbamate 100 mg	*n*	59	46				
	Median	12.1	17.1				
	Range	–213 to 85	–80 to 85				
	P-value[a]	0.959	0.058				
Carisbamate 200 mg	*n*			113	74	116	70
	Median			13.3	26.3	18.0	23.0
	Range			–190 to 100	–102 to 100	–196 to 100	–280 to 93
	P-value[a]			0.792	0.237	0.218	0.283
Carisbamate 300 mg	*n*	69	37				
	Median	25.0	18.4				
	Range	–106 to 100	–540 to 100				
	P-value[a]	0.012	0.070				
Carisbamate 400 mg	*n*			106	85	107	74
	Median			20.4	34.1	17.9	25.6
	Range			–179 to 100	–262 to 100	–692 to 100	–278 to 100
	P-value[a]			0.301	0.003	0.276	0.121
Carisbamate 800 mg	*n*	68	40				
	Median	24.3	17.7				
	Range	–182 to 80	–113 to 84				
	P-value[a]	0.200	0.043				
Carisbamate 1600 mg	*n*	63	42				
	Median	28.2	31.9				
	Range	–284 to 75	–99 to100				
	P-value[a]	0.050	0.007				

I, subjects co-medicated with enzyme-inducing drugs; NI, subjects co-medicated with non-enzyme-inducing drugs.

[a]Pairwise comparison of carisbamate treatment group versus placebo from Wilcoxon rank sum test.

Two subsequent studies, identical in design, evaluated the safety and efficacy of daily dosages of 200 and 400 mg added to one or two concomitant AEDs in patients over 16 years of age ($n = 565$ in study 2 and 562 in study 3) [19]. In study 2, median duration of epilepsy was 19 years; median number of prior AED exposures was five (and 16% had 10 or more); 77% of patients were receiving two concomitant AEDs; and median seizure rate during the prospective 8-week baseline period was 9 per 28 days (range, 2–626). In study 3, median duration of epilepsy was 15 years; median number of prior AED exposures was four (and 8% had 10 or more); 69% of patients were receiving two concomitant AEDs; and median seizure rate during the baseline period was 7 per 28 days (range, 2–279). Subjects attained their target dosage immediately after randomization as there was no titration period. The chief outcome variables were per cent reduction in partial-onset seizure rate in the double-blind treatment phase compared with baseline (comparing each dose with placebo using a Wilcoxon rank sum test stratified by country and adjustment for multiplicity using a stepwise procedure) and responder rate (compared each dose with placebo using the generalized Cochrane–Mantel–Haenszel test controlling for country, with a stepwise adjustment for multiplicity). Most patients completed the double-blind treatment phase (93% in study 2 and 94% in study 3). Efficacy was demonstrated for both outcome variables for the 400-mg dosage only in study 2, but not in study 3. Efficacy outcomes for the 200-mg daily dosage did not differ from placebo in either study (Figs 37.1 and 37.2).

Since the clearance of carisbamate is increased by carbamazepine and phenytoin, drugs that are known to induce uridine glucuronosyltransferase (UGT), the efficacy of carisbamate in the presence and in the absence of UGT-inducing AEDs was analysed. Phenytoin, carbamazepine and phenobarbital were considered significant UGT inducers. Although little difference in efficacy (relative to placebo) between induced and non-induced subgroups was observed in study 1, a different pattern of results was seen in studies 2 and 3 (Tables 37.2 and 37.3). For both the 200-mg and 400-mg daily dosages, in both of these studies, non-induced subjects had a greater reduction in seizure rate and a greater responder rate than induced subjects. These findings suggest that the effects of induction status on exposure may have had an

Table 37.3 Responder rates (patients with ≥50% reduction from baseline in partial-onset seizure frequency) by treatment group in relation to enzyme induction status in three randomized parallel-group placebo-controlled adjunctive therapy studies of carisbamate in patients with refractory partial epilepsy (intent-to-treat analysis set).

Treatment group and daily dose		Study 1		Study 2		Study 3	
		I	NI	I	NI	I	NI
Placebo	Total *n*	62	47	94	89	117	71
	Responder *n*	9	2	18	15	22	18
	Responder rate (%)	14.5	4.3	19.1	16.9	18.8	25.4
Carisbamate 100 mg	Total *n*	59	46				
	Responder *n*	7	6				
	Responder rate (%)	11.9	13.0				
	P-value[a]	0.668	0.133				
Carisbamate 200 mg	Total *n*			113	74	116	70
	Responder *n*			26	21	24	19
	Responder rate (%)			23.0	28.4	20.7	27.1
	P-value[a]			0.500	0.078	0.718	0.810
Carisbamate 300 mg	Total *n*	69	37				
	Responder *n*	19	6				
	Responder rate (%)	27.5	16.2				
	P-value[a]	0.071	0.065				
Carisbamate 400 mg	Total *n*			106	85	107	74
	Responder *n*			31	32	21	22
	Responder rate (%)			29.2	37.6	19.6	29.7
	P-value[a]			0.098	0.002	0.876	0.557
Carisbamate 800 mg	Total *n*	68	40				
	Responder *n*	11	9				
	Responder rate (%)	16.2	22.5				
	P-value[a]	0.794	0.011				
Carisbamate 1600 mg	Total *n*	63	42				
	Responder *n*	10	16				
	Responder rate (%)	15.9	38.1				
	P-value[a]	0.833	<0.001				

I, subjects co-medicated with enzyme-inducing drugs; NI, subjects co-medicated with non-enzyme-inducing drugs.

[a] Pairwise comparison of carisbamate treatment group versus placebo from generalized Cochran–Mantel–Haenszel test for non-zero correlation.

impact on efficacy in the lower dosage range used in the latter studies.

Adverse effects

In study 1, carisbamate has been shown to be safe and well tolerated at all dose levels tested [20]. The most frequently reported treatment-emergent adverse events across all carisbamate treatment groups were headache (n = 128, 30%), dizziness (n = 66, 15%), somnolence (n = 58, 14%) and nausea (n = 47, 11%). Some adverse events were elicited with greater frequency only at the highest dose. These included headache, diplopia, vertigo, vomiting, gait disturbance and abnormal coordination, occurring more commonly in the 1600 mg/day group than in all other groups. None of the other carisbamate dose groups differed by more than 5% from placebo for these adverse events. Three other adverse events appeared to be dose related: nausea (incidence more than 5% greater than placebo for doses ≥800 mg/day), dizziness (for doses ≥300 mg/day) and somnolence (all doses) (Fig. 37.3) [18]. Notably, no cognitive or behavioural adverse events occurred more commonly than placebo. The frequency of rash was low: 4% of placebo-treated and 2% of carisbamate-treated patients overall. Discontinuation rates in the carisbamate dose groups were low. Adverse events that resulted in discontinuation occurred in 8% of the placebo group, and 5% (100 mg/day), 6% (300 mg/day), 12% (800 mg/day) and 19% (1600 mg/day) of the carisbamate dose groups. For patients treated with carisbamate, dizziness [n = 8 (2%)] and headache [n = 7 (2%)] were the most common adverse events leading to withdrawal, with the majority of reports occurring in the 1600 mg/day group. Two or fewer patients in any other dose group withdrew as a result of these adverse events [18].

The tolerability of the 200-mg and 400-mg daily dosages in studies 2 and 3 was comparable to placebo. Among the common adverse events (≥5% in any group), only two occurred more frequently for carisbamate than for placebo: dizziness (for 400 mg/day: 12% and 13% in studies 2 and 3, respectively versus 7% for placebo in both studies) and somnolence (for 400 mg/day: 5% and 9%, respectively; for placebo: 4% and 1%, respectively).

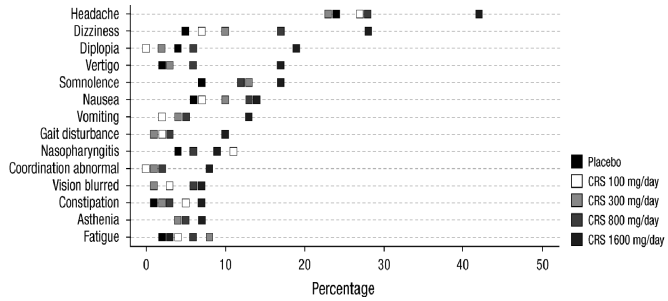

Fig. 37.3 Percentage of patients reporting treatment-emergent adverse events in a randomized parallel-group placebo-controlled adjunctive therapy trial which explored carisbamate (CRS) dosages between 100 and 1600 mg/day in patients with refractory partial epilepsy (study 1, safety analysis population). Only adverse events reported by at least 7% of patients in any carisbamate group are shown. Reproduced from ref. 20 with permission.

Rates of discontinuation because of adverse events were no more than 5% in any treatment group, and were similar for placebo and for both dosages of carisbamate.

Across all three placebo-controlled trials, serious adverse events occurred with approximately equal frequency for placebo (n = 19/496 patients, 3.8%) and for carisbamate (40/1213, 3.3%; range, 3–5% for any dosage). The most common serious adverse events have been injuries (placebo, 5/496, 1.0%; carisbamate, 9/1213, 0.7%) and seizure related (placebo, 10/496, 2.0%; carisbamate, 7/1213, 0.6%). The only serious adverse events that occurred in more than one subject were status epilepticus (placebo, five subjects), psychosis (carisbamate, three subjects), toxic hepatitis (carisbamate, two subjects) and hyponatraemia (carisbamate, two subjects). No deaths were reported. No patients had a serious drug-related rash.

Elevations of serum alanine aminotransferase (ALT) three times above normal values occurred in six patients treated with carisbamate in these three trials, with an apparent dose relationship: placebo, 0/496; pooled carisbamate 100–300 mg/day, 0/586; carisbamate 400 mg/day, 2/377 (0.5%); carisbamate 800 mg/day, 1/108 (0.9%); and carisbamate 1600 mg/day, 3/105 (2.9%). These patients were asymptomatic, and all ALT elevations resolved, in some cases with continued treatment with carisbamate at the same or lower dosage. There were no other patterns of clinically significant abnormalities in laboratory evaluations in these studies [20].

Summary and preliminary assessment of therapeutic potential

Carisbamate is a novel AED that has demonstrated broad-spectrum anticonvulsant activity in preclinical studies. Preclinical studies also suggested that carisbamate may be a useful treatment for other neurological conditions, such as neuropathic pain.

In humans, carisbamate shows linear pharmacokinetics, virtually complete absorption from the gastrointestinal tract, a half-life compatible with twice-daily dosing and extensive metabolism, primarily by glucuronide conjugation, with less than 2% excreted in the urine in unchanged form. Studies also suggest that carisbamate possesses a low potential for the formation of reactive metabolites. Extensive evaluations of potential drug–drug interactions have revealed that carisbamate has a low propensity to alter the pharmacokinetics of co-administered drugs. With respect to the co-administration of other AEDs, carisbamate causes a slight and clinically insignificant decrease in the levels of lamotrigine, and no significant interaction with valproic acid. Of clinical importance, however, is the fact that AEDs which induce UGTs, such as carbamazepine, phenytoin, phenobarbital and primidone, have the potential to reduce the plasma concentration of carisbamate.

Three randomized controlled trials have provided evidence supporting the efficacy of carisbamate at doses of 300–1600 mg/day as adjunctive treatment in highly refractory patients with partial-onset seizures. At efficacious dosages of 300 mg/day, 400 mg/day and 800 mg/day, the compound displayed a favourable adverse event profile resulting in an overall low discontinuation rate, and no or only limited cognitive and behavioural/psychiatric side-effects. The most frequently reported treatment-emergent adverse events in clinical trials have been headache, dizziness, somnolence and nausea.

Results from further ongoing clinical trials will allow us to define in more detail the therapeutic potential of carisbamate in the treatment of epilepsy.

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38 Eslicarbazepine Acetate

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Primary indication	Adjunctive therapy of partial seizures (potential additional indications are under assessment)
Usual preparation	Tablets: 400 mg, 600 mg and 800 mg Suspension: 50 mg/mL
Usual dosage	800–1200 mg/day (tentative dose range)
Dosing frequency	Once daily
Significant drug interactions	Enzyme-inducing antiepileptic drugs decrease plasma eslicarbazepine levels. Eslicarbazepine acetate decreases the plasma levels of steroid oral contraceptives
Serum level monitoring	There is insufficient information on the value of monitoring serum eslicarbazepine levels
Reference range	Not established as yet
Common/important adverse effects	Dizziness, blurred vision, diplopia, visual disturbances, nausea and vomiting, fatigue, incoordination, headache, somnolence
Main advantages	Usually well tolerated, once-daily dosing
Main disadvantages	Limited clinical experience. Efficacy spectrum probably restricted to partial epilepsies
Mechanism of action	Blockade of voltage-gated sodium channels[a]
Oral bioavailability	Almost complete (in terms of the active metabolite eslicarbazepine)
Time to peak levels	2–3 h[a]
Metabolism and excretion	Hydrolysed rapidly to eslicarbazepine, which is excreted in urine in free and conjugated form. Minor metabolites include (*R*)-licarbazepine, oxcarbazepine and their conjugates
Volume of distribution	About 2.7 L/kg[a]
Elimination half-life	13–20 h[a]
Plasma clearance	About 55 mL/h/kg
Protein binding	30%[a]
Active metabolites	Eslicarbazepine. Minor active metabolites include oxcarbazepine and (*R*)-licarbazepine
Comment	Potentially a useful antiepileptic drug, but more data are needed to establish its place in current therapy

[a] Pharmacokinetic parameters refer to eslicarbazepine, for which eslicarbazepine acetate can be considered a prodrug.

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Introduction

Eslicarbazepine acetate (BIA 2-093) is a novel voltage-gated sodium channel blocker that was identified as a promising candidate for clinical development through a drug discovery programme initiated in the mid-1990s by Bial (Portela & Co., S.A.) [1]. Eslicarbazepine acetate was designed to be a single (*S*)-enantiomer member of the established family of dibenz[b,f]azepine derivatives represented by carbamazepine and oxcarbazepine [2]. In its chemical structure, eslicarbazepine acetate shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute, but it is structurally different at the 10,11-position [3]. This molecular variation results in differences in metabolism [4]. Unlike carbamazepine, eslicarbazepine acetate is not metabolized to carbamazepine-10,11-epoxide and is not susceptible to metabolic autoinduction. Unlike oxcarbazepine, which is a prochiral prodrug metabolized presystemically to both eslicarbazepine [also called (*S*)-licarbazepine or (*S*)-MHD] and (*R*)-licarbazepine [also called (*R*)-MHD] [5], eslicarbazepine acetate is a prodrug of only eslicarbazepine, which is the active entity responsible for eslicarbazepine acetate pharmacological effects in humans.

This chapter will review preclinical and clinical pharmacokinetic, efficacy and safety data of eslicarbazepine acetate in epilepsy. Studies in other indications (neuropathic pain, fibromyalgia and migraine prophylaxis) are currently ongoing.

Chemistry

Eslicarbazepine acetate corresponds chemically to (*S*)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (Fig. 38.1). Its molecular formula is $C_{17}H_{16}N_2O_3$ and its molecular weight is 296.32. Eslicarbazepine acetate is a white to off-white, odourless and non-hygroscopic, crystalline powder with a melting point of 184–187°C. Eslicarbazepine acetate is very slightly soluble (<1 mg/mL) in aqueous buffer solutions at different pH; its intrinsic dissolution is within 0.06 and 0.07 mg/min/cm^2 for a pH in the range of 1.2–6.8. Eslicarbazepine acetate is freely soluble in dichloromethane, sparingly soluble in acetone, acetonitrile, methanol and tetrahydrofuran, and slightly soluble in absolute ethanol and 2-propanol. Eslicarbazepine acetate is a neutral compound and as such it is non-ionizable at physiological conditions.

The structure of eslicarbazepine acetate has been determined and confirmed by elemental analysis, ultraviolet, infrared, mass and nuclear magnetic resonance spectroscopy. Eslicarbazepine acetate is a thermally stable and photostable substance. Eslicarbazepine acetate's physical appearance and chromatographic behaviour remain unchanged at a storage temperature of 30°C and relative humidity (RH) of 65% for up to 3 years as well as under accelerated conditions of 40°C/75% RH for 6 months.

Plasma and urine concentrations of eslicarbazepine acetate and its metabolites can be monitored by solid-phase extraction followed by high-performance liquid chromatography (HPLC), with ultraviolet or mass spectrometric detection [6–12].

Pharmacokinetic and activity profile in animal models and mechanisms of action

Pharmacokinetic differences across species

Eslicarbazepine acetate disposition varies significantly across species. In general, following oral administration to animals or humans, no or minimal measurable concentrations of the parent drug (eslicarbazepine acetate) were observed. In the rat, eslicarbazepine acetate was mainly metabolized to oxcarbazepine, with eslicarbazepine and (*R*)-licarbazepine as minor metabolites. In the mouse, the hamster and the rabbit, eslicarbazepine was the major metabolite and oxcarbazepine and (*R*)-licarbazepine were minor metabolites. In the Beagle dog, eslicarbazepine was a major metabolite and oxcarbazepine and (*R*)-licarbazepine were minor metabolites, but measurable amounts of eslicarbazepine acetate were observed up to 2 h after administration. In the cynomolgus monkey, measurable amounts of eslicarbazepine acetate were found up to 1.5 h after administration, with eslicarbazepine representing up to 96.5% of active moieties; no measurable amounts of oxcarbazepine and (*R*)-licarbazepine were found. In humans, eslicarbazepine

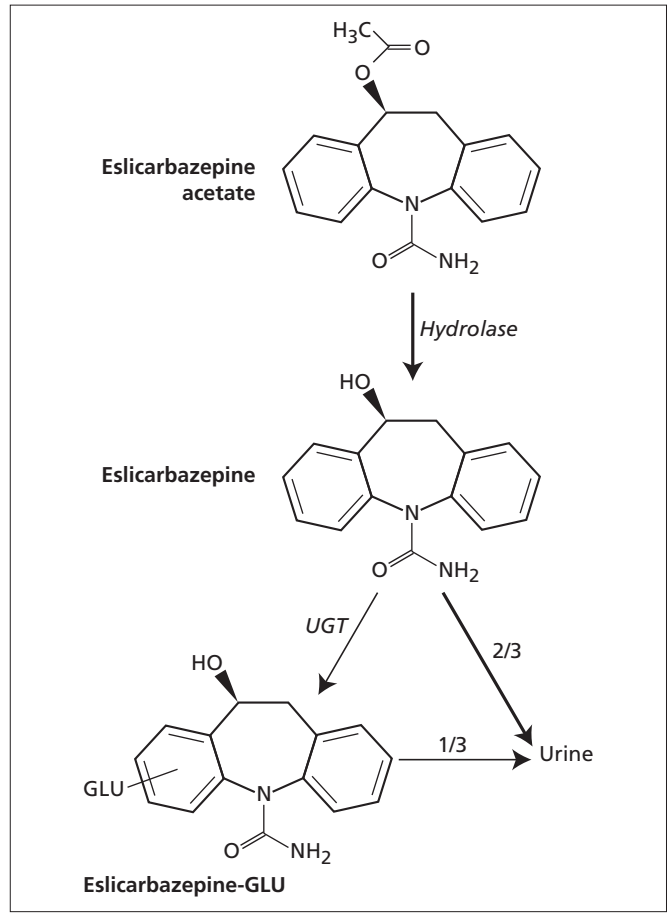

Fig. 38.1 Main metabolic and elimination pathway of eslicarbazepine acetate following oral administration to humans. More than 90% of an eslicarbazepine acetate dose is excreted in urine as eslicarbazepine [two-thirds in unconjugated form and one-third as a glucuronide conjugate (-GLU)]. UGT, uridine diphosphate-5′-glucuronosyltransferase.

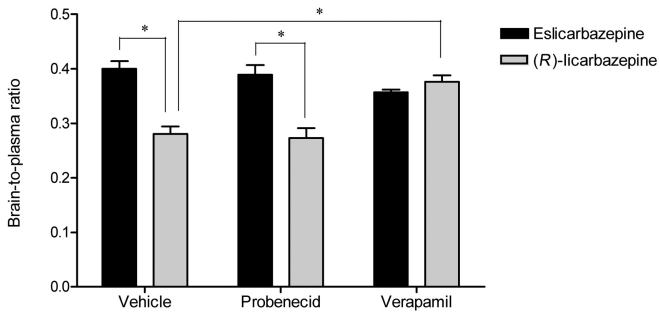

Fig. 38.2 Brain-to-plasma concentration ratios of eslicarbazepine and (*R*)-licarbazepine in nuclear magnetic resonance imaging mice pretreated with vehicle, probenecid (100 mg/kg, p.o.) or verapamil (20 mg/kg, p.o.) and subsequently (30 min later) given eslicarbazepine or (*R*)-licarbazepine (100 mg/kg, i.p.). Samples were collected at 1 h post dose. Columns indicate means of five determinations per group; vertical lines indicate the corresponding SEM. $*P < 0.05$.

acetate was extensively metabolized mainly to eslicarbazepine; (*R*)-licarbazepine and oxcarbazepine were minor metabolites [13].

In the mouse, following the administration of eslicarbazepine or (*R*)-licarbazepine, the ratio of the areas under the concentration–time curves (AUC) in brain ($AUCbrain_{eslicarbazepine}$/$AUCbrain_{(R)\text{-licarbazepine}}$) was greater than AUC ratios in plasma ($AUCplasma_{eslicarbazepine}$/$AUCplasma_{(R)\text{-licarbazepine}}$; 1.87 versus 1.10), suggesting that distribution of eslicarbazepine into the brain is more extensive than that for (*R*)-licarbazepine [14]. It is thus apparent that (*R*)-licarbazepine has considerably more difficulty penetrating the brain. In fact, the brain-to-plasma ratio for eslicarbazepine, considering either the peak concentration (C_{max}) or AUC, was found to be twice as high as that for (*R*)-licarbazepine [14]. This clearly indicates that there is enantioselectivity in crossing the blood–brain barrier.

To assess whether differences in brain penetration of eslicarbazepine and (*R*)-licarbazepine were related to susceptibility for efflux through P-glycoprotein (P-gp) or multidrug resistance protein (MRP), mice were pretreated with verapamil or probenecid [13]. As shown in Figure 38.2, verapamil and probenecid failed to affect the eslicarbazepine brain-to-plasma concentration ratio. By contrast, verapamil, but not probenecid, markedly increased the (*R*)-licarbazepine brain-to-plasma ratio. This indicates that eslicarbazepine is not a substrate for either P-gp or MRP, whereas (*R*)-licarbazepine is a substrate for P-gp but not for MRP. It is interesting to note that the (*R*)-licarbazepine brain-to-plasma ratio after verapamil treatment was equal to that of eslicarbazepine in vehicle-treated animals. These findings are in line with previous evidence that racemic (*R*,*S*)-licarbazepine appears to cross the blood–brain barrier not by simple passive diffusion, but rather by a P-gp-mediated active transport [15]. Since eslicarbazepine and (*R*)-licarbazepine have different pharmacodynamic and pharmacokinetic properties, they should be evaluated individually utilizing enantiospecific methods.

Mechanisms of action and activity in experimental models

The precise mechanism of action of eslicarbazepine acetate and eslicarbazepine is unknown. However, *in vitro* electrophysiological studies indicate that eslicarbazepine acetate and eslicarbazepine inhibit sodium currents in a voltage-dependent way by competitively interacting with the inactivated voltage-gated sodium channels, thereby preventing their return to the active state. Eslicarbazepine acetate and eslicarbazepine interact with the neurotoxin receptor site 2 of the voltage-gated sodium channel, but not with receptor site 1 [16]. Eslicarbazepine acetate inhibits sodium currents in a voltage-dependent way by interacting predominantly with the inactivated state of the channel in mouse neuroblastoma cell line N1E-115. Over the range of neuronal resting membrane potentials likely to be encountered in the brain *in situ*, eslicarbazepine acetate displayed a similar inhibitory potency to carbamazepine [16]. Eslicarbazepine, (*R*)-licarbazepine and oxcarbazepine also inhibited voltage-gated sodium channels in neuroblastoma N1E-115 cells. The potency of inhibition was highly sensitive to the holding potential, increasing with depolarization. For each different holding potential, carbamazepine exhibited the highest inhibitory potential (Table 38.1). All compounds had a much higher affinity for the inactivated (K_I) state of the channel, but the affinities of eslicarbazepine acetate, eslicarbazepine and (*R*)-licarbazepine were approximately two-, four- and four-fold lower than that of carbamazepine, respectively. The affinities of these compounds for the resting (K_R) state of N1E-115 endogenous sodium channels (calculated based on the fits of the voltage dependence of the channel availability) differed significantly. However, no significant difference was found concerning the affinity of carbamazepine and oxcarbazepine for the inactivated state of the channel. The affinity of eslicarbazepine for sodium channels in the resting state was about 15- to 5-fold lower than that of carbamazepine, oxcarbazepine and (*R*)-licarbazepine, a feature that may translate into an enhanced inhibitory selectivity of eslicarbazepine for rapidly firing 'epileptic' neurones over those with normal activity [17].

Table 38.1 Comparative affinities of eslicarbazepine acetate, its metabolites and carbamazepine for the resting (K_R) and inactivated (K_I) state of the sodium channel. Results are means ± SEM of four to five experiments.

Compound	Affinity (μmol)	
	K_R	K_I
Carbamazepine	1410 ± 598	74 ± 20
Oxcarbazepine	2964 ± 699	67 ± 8
Eslicarbazepine acetate	10166 ± 7291	146 ± 77
Eslicarbazepine	21006 ± 4497	245 ± 37
(*R*)-licarbazepine	3843 ± 825	285 ± 53

Eslicarbazepine acetate was tested in several models predictive of anticonvulsant efficacy, such as the maximal electroshock seizure (MES) test in rats and mice and the corneal kindling in mice [13]. In the MES test, eslicarbazepine, acetate was found to be equally potent to carbamazepine, and more potent than oxcarbazepine, 2 h and 4 h after administration by gastric tube; 8 h after administration the drugs were equipotent [3]. In NMRI mice, eslicarbazepine acetate (administered orally 60 min before the test) significantly decreased the number of tonic convulsions observed in the MES test at all doses (10, 25, 50, 75, 100 and 150 mg/kg) (Fig. 38.3). With the exception of one measurable sample at 100 mg/kg, eslicarbazepine acetate was not detected in plasma 60 min after dosing. Since eslicarbazepine acetate is extensively metabolized by first-pass effect to eslicarbazepine,

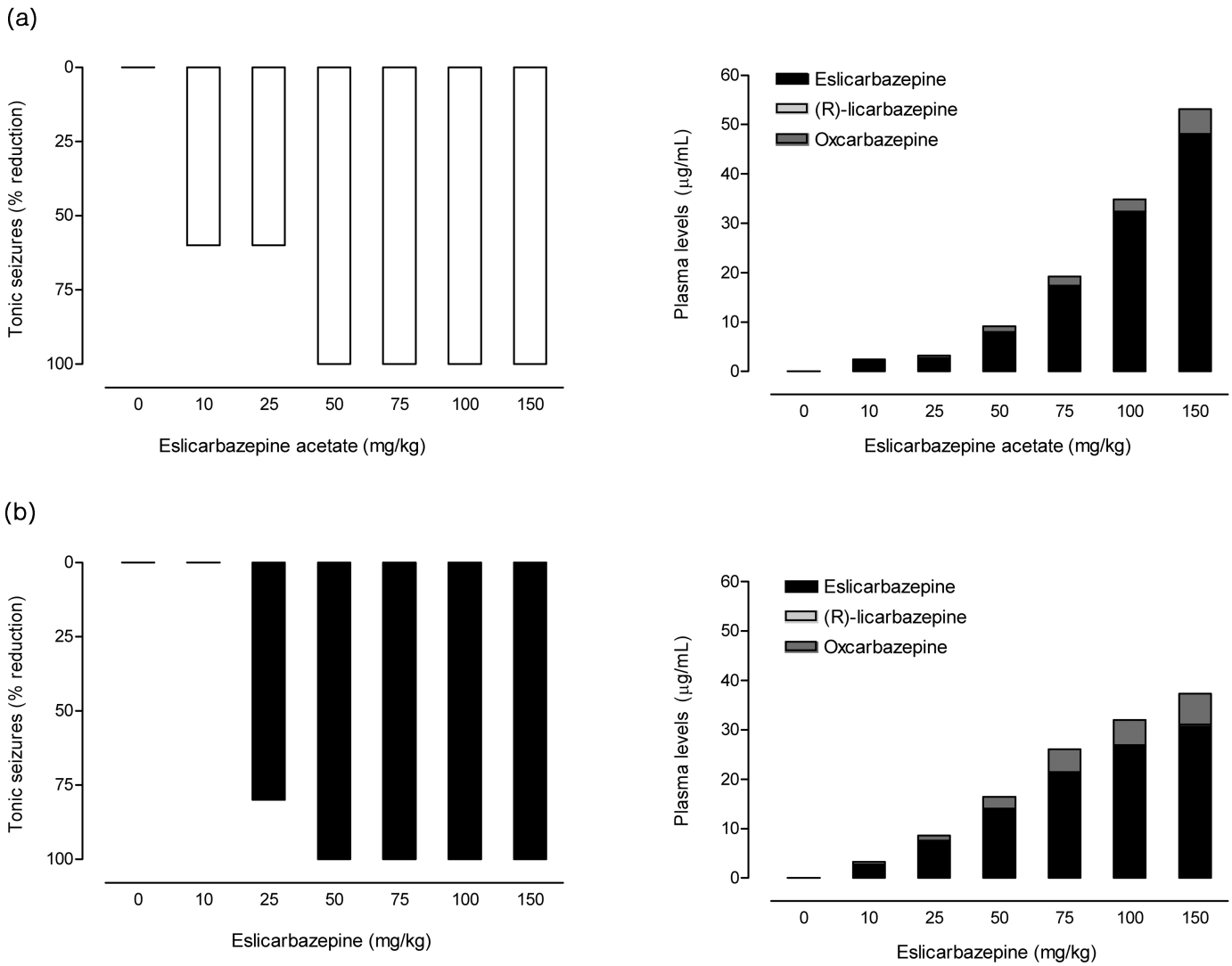

Fig. 38.3 Anticonvulsant effects in the maximal electroshock (MES) test (left panels) and plasma concentrations of eslicarbazepine acetate metabolites (right panels) 1 h after p.o. administration of eslicarbazepine acetate (a) or eslicarbazepine (b) in the mouse.

which represented approximately 90% of the systemic drug exposure (AUC), the anticonvulsant activity observed with eslicarbazepine acetate can be attributed to the activity of eslicarbazepine. Administration of eslicarbazepine at 25 mg/kg and above (50, 75, 100 and 150 mg/kg) also significantly decreased the number of tonic convulsions in the MES test. The concentrations of eslicarbazepine increased with increasing dose of eslicarbazepine acetate in all mice.

The effects of eslicarbazepine acetate were also evaluated in the 6-Hz psychomotor seizure model in the mouse [13]. In the first set of experiments, eslicarbazepine acetate was tested at 1, 2.5, 5, 10, 25 and 50 mg/kg, administered orally 30 min before the test (44 mA, 3 s, 0.2 ms pulse width, 6 Hz, via corneal electrodes). The seizure score (maximum possible score = 2) was significantly decreased at 2.5, 5 and 10 mg/kg (–0.5, $P < 0.05$), at 25 mg/kg (–0.5, $P < 0.01$) and at 50 mg/kg (–1.0, $P < 0.001$) compared with the vehicle control. In another set of experiments, eslicarbazepine acetate was tested at 5, 10, 25, 50, 100 and 150 mg/kg, administered orally 60 min before the test (rectangular current: 32 mA, 3 s, 0.2 ms pulse width, 6 Hz, via corneal electrodes). All of these doses of eslicarbazepine acetate decreased forelimb seizure score compared with vehicle control. The seizure score decreased significantly for all doses between 10 mg/kg and 150 mg/kg (10 mg/kg: –0.4, $P < 0.05$; 25 mg/kg: –0.4, $P < 0.05$; 50 mg/kg: –0.6, $P < 0.05$; 100 mg/kg: –1.3, $P < 0.001$; and 150 mg/kg: –1.0, $P < 0.001$).

In NMRI mice, eslicarbazepine acetate significantly retarded kindling development (Fig. 38.4) [18]. At dosages of 30 and 100 mg/kg eslicarbazepine acetate, the average number of stimulations to reach a fully kindled generalized seizure was increased by 217% and 280%, respectively. These data provide evidence for an anticonvulsant effect of eslicarbazepine acetate on partial-onset seizures. However, disease-modifying effects may also be involved. Eslicarbazepine acetate may not merely suppress seizure activity but may also inhibit the generation of a hyperexcitable network and therefore provide an antiepileptogenic effect [18]. Administration of eslicarbazepine also had an inhibitory effect on acquisition of kindling, whereas (*R*)-licarbazepine did not affect

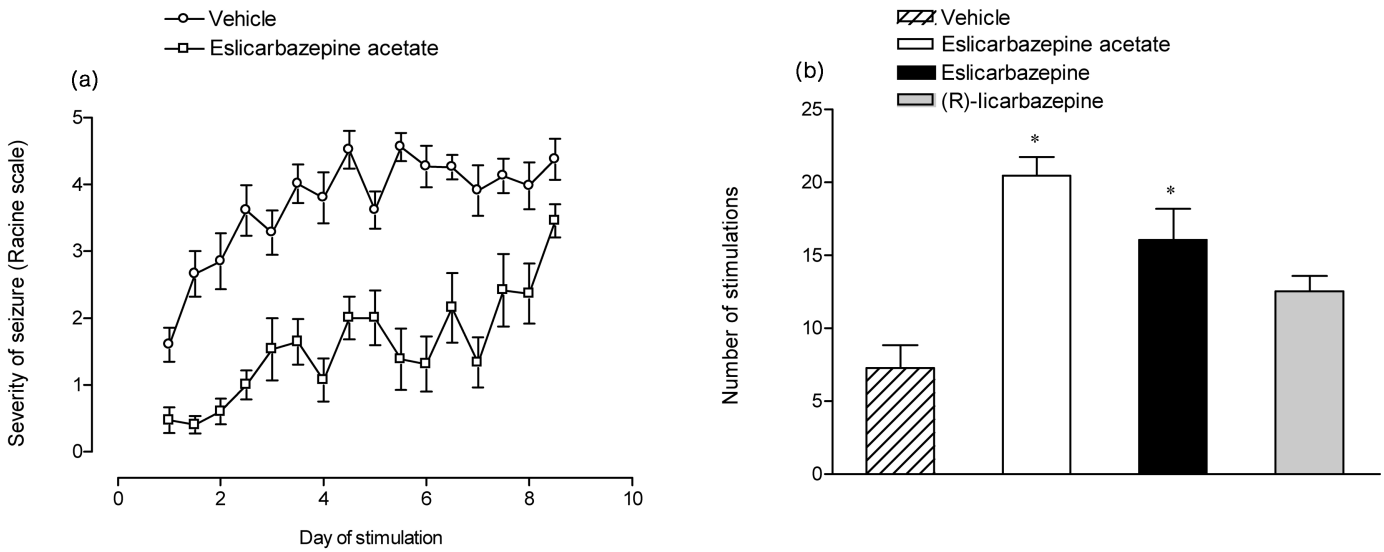

Fig. 38.4 (a) Effect of twice-daily eslicarbazepine acetate (100 mg/kg, i.p.) for 12 days on acquisition of kindling (i.e. development of seizure severity) upon repeated transcorneal stimulation. (b) Effects of twice-daily eslicarbazepine acetate (100 mg/kg, i.p.), eslicarbazepine (100 mg/kg, i.p.) and (*R*)-licarbazepine (100 mg/kg, i.p.) for 12 days on the number of stimulations necessary to induce a seizure with a severity score of 5 on the Racine scale in the mouse corneal kindling model. Mice were stimulated twice daily (inter-stimulation interval 6–7 h) on 12 consecutive days. Data are mean values ± SEM. $*P < 0.05$ versus vehicle.

the number of stimulations necessary to induce a specific seizure stage, and did not exert any relevant effect on mean seizure severity during kindling progression (Fig. 38.4).

Oral treatment with eslicarbazepine acetate was also tested in an animal model in which partial seizures can be elicited repeatedly on different days without changes in threshold or seizure patterns [19]. In rats treated with threshold doses of picrotoxin (perfused through the hippocampus), the average number of seizures was 2.3 ± 1.2, and average seizure duration was 39.5 ± 8.4 s. Pretreatment with eslicarbazepine acetate (30 mg/kg) 2 h before picrotoxin microperfusion prevented seizures in 75% of the rats. Lower doses of eslicarbazepine acetate (3 and 10 mg/kg) did not completely suppress seizures; however, after 10 mg/kg, significant reductions in seizure duration (24.3 ± 6.8 s) and seizure number (1.6 ± 0.3) were observed. No adverse effects of eslicarbazepine acetate were observed in the behavioural/EEG patterns studied, including sleep–wakefulness cycle, at the doses tested. Eslicarbazepine acetate also protected against seizures induced in rats and mice by the chemoconvulsants metrazole, bicuculline, picrotoxin and 4-aminopyridine [20].

Intrahippocampal microperfusion of latrunculin A (4 μmol) induces long-term changes in neuronal excitability leading to onset of sporadic spontaneous seizures [21]. Oral doses of eslicarbazepine acetate 10 and 30 mg/kg resulted in marked attenuation of seizures induced by latrunculin A microperfusion in the rat hippocampus. The molecular mechanisms behind latrunculin A seizures are still unknown, but the increase in extracellular glutamate concentrations observed during latrunculin A microperfusion are completely reversed by eslicarbazepine acetate. This fits well with the observation that eslicarbazepine acetate is a potent blocker of the 4-aminopyridine-evoked [22] or veratridine-evoked [23] release of glutamate.

In comparison with carbamazepine and oxcarbazepine, eslicarbazepine acetate causes less neurological impairment in rats and mice following intraperitoneal administration and, consequently, it has a higher protective index ($PI = TD_{50}/ED_{50}$). In a study in which cultured hippocampal neurones were treated for 24 h with carbamazepine or oxcarbazepine (300 μmol), the neurones showed degeneration and swelling of neurites, but this effect was not observed in neurones treated with eslicarbazepine acetate (300 μmol) [24].

Toxicology

There have been no findings considered to be of concern for human use based on conventional preclinical studies of safety, pharmacology, toxicology, genotoxicity, reprotoxicity and carcinogenicity. In acute toxicology studies, eslicarbazepine acetate oral LD_{50} values were 500 mg/kg (mice and rats) and 100 mg/kg (mice) and <50 mg/kg (rats) when administered by an intravenous bolus. An increase in activated partial thromboplastin time (aPTT) was reported in chronic toxicity studies in Beagle dogs, but no similar change was reported in other species, including humans. An increase in plasma cholesterol was reported in rats and dogs but not in other species, including humans.

Clinical pharmacokinetics

Eslicarbazepine acetate is currently available in the form of tablets and suspension for oral administration. Its clinical pharmacokinetics has been studied following oral administration to healthy young and elderly adults, adults and paediatric patients with epilepsy, and patients with renal and hepatic impairment.

Pharmacokinetics in healthy subjects and patients with epilepsy

Following oral administration to humans, eslicarbazepine acetate is rapidly and extensively biotransformed to eslicarbazepine by

first-pass hydrolytic metabolism [7]. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification. The bioavailability of eslicarbazepine following oral administration of eslicarbazepine acetate is high and >90% of an orally administered eslicarbazepine acetate dose is recovered as metabolites in urine [7]. The pharmacokinetics of eslicarbazepine acetate is unaffected by the presence of food [25].

At concentrations up to 100 μg/mL (about twice its C_{max} at steady state following eslicarbazepine acetate multiple dosing of 2400 mg once daily) [26], the plasma protein binding of eslicarbazepine is on average 30%, and its binding to blood cells is 46%. Eslicarbazepine binding to plasma proteins and blood cells is concentration independent. Eslicarbazepine binding to plasma proteins was unaffected by warfarin, diazepam, digoxin, phenytoin and tolbutamide. Similarly, the binding of [^{14}C]warfarin, [^{14}C]diazepam, [^{3}H]digoxin, [^{14}C]phenytoin and [^{14}C]tolbutamide was not significantly affected by the presence of eslicarbazepine [17].

For the quantification of eslicarbazepine acetate metabolites in plasma or urine, achiral and chiral methods have been used in pharmacokinetic studies. When a chiral method is used, the assay distinguishes between eslicarbazepine and its minor metabolite (*R*)-licarbazepine [7,10,12]. When an achiral method is used, the assay does not allow the separation of eslicarbazepine and (*R*)-licarbazepine, and the enantiomeric mixture has been reported as BIA 2-005 [8,9].

After single oral doses of eslicarbazepine acetate ranging from 20 mg to 1200 mg, approximately dose-proportional increase in BIA 2-005 C_{max} and a greater than dose-proportional increase in its AUC have been found [8]. The half-life of BIA 2-005 ranged between 9 h with eslicarbazepine acetate 20 mg and 17 h with eslicarbazepine acetate 1200 mg. Oxcarbazepine was shown to be a minor metabolite in both plasma and urine, representing approximately 1% of plasma exposure (AUC) to BIA 2-005 [8].

Following repeated oral dosing of eslicarbazepine acetate 400 mg, 800 mg and 1200 mg once daily to healthy subjects, peak plasma BIA 2-005 concentrations were reached 2.5–3 h after drug intake. Thereafter, plasma BIA 2-005 concentrations declined with an apparent half-life ranging between 10 h (400 mg once daily) and 13 h (1200 mg once daily) [9]. During multiple dosing, peak plasma BIA 2-005 concentrations and AUC values during a dosing interval at steady state increased in an approximately dose-proportional manner. The mean observed accumulation ratio (R_{ac}) or accumulation index of BIA 2-005 was 1.4–1.7 following 400–1200 mg once-daily dosing, consistent with an effective half-life in the order of 20–24 h, calculated from the quotient $R_{ac} = 1/(1 - \exp^{-\lambda z.\tau})$ where λ_z is the linear terminal slope of the log-plasma concentration versus time plot and τ is the dosing interval [27]. Steady-state plasma concentrations of BIA 2-005 were reached 4–5 days after repeated eslicarbazepine acetate dosing, which is also consistent with an effective half-life of 20–24 h.

In a group of healthy subjects administered eslicarbazepine acetate 800 mg once daily, the chiral method was used to monitor plasma and urine levels of eslicarbazepine acetate and its metabolites as free (unconjugated) and glucuronide conjugates [7]. The mean plasma concentrations of eslicarbazepine acetate and its metabolites during a 24-h dosing interval at steady state are shown in Figure 38.5. Using AUC_{ss} as a measure of systemic exposure, eslicarbazepine corresponded to approximately 91% of the sum of all circulating eslicarbazepine acetate-related entities (parent compound and metabolites). The minor metabolites in plasma [(*R*)-licarbazepine, oxcarbazepine and glucuronide conjugates of eslicarbazepine, (*R*)-licarbazepine and oxcarbazepine] corresponded to 9% of total systemic exposure [7]. The main eslicarbazepine acetate metabolic pathways, based on these data, are illustrated in Figure 38.1.

In 51 adults with epilepsy treated with eslicarbazepine acetate 400 mg (n = 7), 800 mg (n = 26) or 1200 mg once daily (n = 18) concomitantly with one or two AEDs (with carbamazepine being taken by 67% of patients), eslicarbazepine exposure in plasma was roughly dose proportional [13]. Peak eslicarbazepine concentrations at steady state were reached 2 h after eslicarbazepine acetate dosing and declined thereafter in a multiphasic manner, with a mean half-life of 13–20 h. The exposure in plasma of the minor metabolites (*R*)-licarbazepine and oxcarbazepine was also linear and dose proportional.

Trough plasma eslicarbazepine concentrations were determined in 571 adults with epilepsy treated with eslicarbazepine acetate 400 mg (n = 160), 800 mg (n = 222) and 1200 mg (n = 189) once daily concomitantly with one to three antiepileptic drugs (AEDs), with carbamazepine being again the most commonly prescribed co-medication (about 60% of patients) [13]. Mean (95% CI) eslicarbazepine trough concentrations at steady state were 2.1 (1.9–2.4) μg/mL with 400 mg, 5.1 (4.5–5.6) μg/mL with 800 mg and 8.1 (7.3–8.9) μg/mL with 1200 mg. In a population pharmacokinetic analysis of data obtained in these patients, eslicarbazepine pharmacokinetics was best described as a one-compartment open model, with a first-order absorption (absorption rate constant, k_a = 1.25 h^{-1}), an apparent volume of distribution (V_d/F) of 188 L and an apparent oral clearance (CL/*F*) of 3.82 L/h. Eslicarbazepine acetate did not affect its own metabolism or clearance and consistently no time dependency was observed in eslicarbazepine pharmacokinetics for up to 1 year of treatment [13].

Eslicarbazepine and other eslicarbazepine acetate metabolites are mainly eliminated in the urine [7,12]. Following multiple dosing of eslicarbazepine acetate (800 mg once daily) to healthy subjects, 92% of the eslicarbazepine acetate dose was excreted in urine as eslicarbazepine, two-thirds (67%) as free (unconjugated) form and one-third (33%) as the glucuronide conjugate [7]. The remaining 8% of the eslicarbazepine acetate dose was excreted in urine as (*R*)-licarbazepine, oxcarbazepine and glucuronide conjugates of eslicarbazepine acetate, eslicarbazepine, (*R*)-licarbazepine and oxcarbazepine.

Pharmacokinetics in special populations

A study in healthy young (18–40 years) and elderly (≥65 years) subjects showed that the pharmacokinetics of eslicarbazepine acetate was not significantly affected by age [6] or gender [10]. Similarly, bioavailability and apparent oral clearance of eslicarbazepine following administration of eslicarbazepine acetate to adults (17–76 years) with epilepsy were not affected by age or gender [13].

The pharmacokinetics of eslicarbazepine acetate in paediatric age were characterized in an open-label phase IIa study which included children with epilepsy aged 2–6 (n = 11) and 7–11 (n = 8) years and adolescents aged 12–17 years (n = 10), treated with one to three concomitant AEDs [28]. The study consisted of three consecutive 4-week periods with once-daily administration

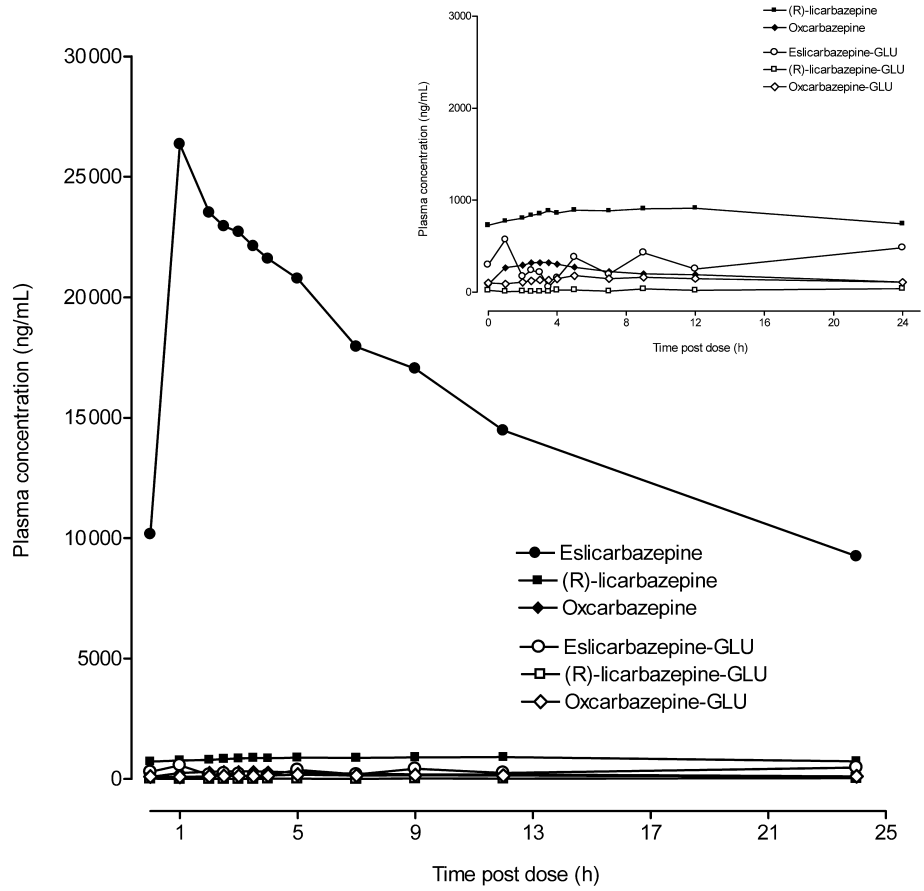

Fig. 38.5 Mean plasma concentration–time profiles during a 24-h dosing interval at steady state of eslicarbazepine acetate metabolites following the last dose of an 8-day treatment with eslicarbazepine acetate 800 mg once daily in eight healthy subjects. GLU, glucuronide conjugate. The inset magnifies the minor metabolites profiles.

of eslicarbazepine acetate 5 mg/kg/day in weeks 1–4, 15 mg/kg/day in weeks 5–8 and 30 mg/kg/day or 1800 mg/day, whichever was less, in weeks 9–12. Similar to adults, eslicarbazepine acetate was rapidly metabolized to eslicarbazepine. In all age groups, eslicarbazepine peak concentrations were reached 1–3 h after eslicarbazepine acetate dosing, and peak concentrations and AUC values at steady state were dose proportional. Eslicarbazepine peak concentrations were similar between age groups following administration of identical eslicarbazepine acetate doses/kg, but AUC values were age dependent due to faster clearance of eslicarbazepine in younger children than in adolescents.

To assess the effect of renal function on eslicarbazepine acetate pharmacokinetics, a study was conducted in which a single dose of eslicarbazepine acetate 800 mg was administered to five groups (n = 8 each): one with normal renal function, three with different degrees of renal dysfunction (mild, moderate and severe) and a fifth with end-stage renal disease requiring haemodialysis [12]. Eslicarbazepine C_{max} did not differ significantly between groups. However, eslicarbazepine $AUC_{0-\infty}$ increased significantly in the mild, moderate and severe renal impairment groups. A significant relationship was found between creatinine clearance (CL_{CR}) and eslicarbazepine renal clearance. The pharmacokinetics of the minor eslicarbazepine acetate metabolites eslicarbazepine glucuronide, (*R*)-licarbazepine, (*R*)-licarbazepine glucuronide, oxcarbazepine and oxcarbazepine glucuronide was also significantly affected by renal function. Tubular reabsorption probably explains the finding that eslicarbazepine renal clearance (7.3 mL/min) was lower than glomerular filtration rate in the subjects with normal renal function (CL_{CR} > 80 mL/min) [12]. The total amount of eslicarbazepine recovered in urine was similar in the groups with normal renal function and mild renal impairment, but was markedly decreased in the moderate and severe renal impairment groups. Major eslicarbazepine acetate metabolites recovered in urine were eslicarbazepine and eslicarbazepine glucuronide. However, in the moderate and severe renal impairment groups, the fraction of eslicarbazepine acetate dose excreted in urine as eslicarbazepine decreased while the fraction excreted as eslicarbazepine glucuronide increased, indicating that renal excretion of eslicarbazepine is more affected than eslicarbazepine glucuronide by renal impairment [12]. Because eslicarbazepine acetate pharmacokinetics is renal function dependent, dose adjustment is required in subjects with renal impairment. Analysis of existing data supports the recommendation of no dose adjustment in patients with a CL_{CR} > 60 mL/min and a half-dose for patients with CL_{CR} of 30–60 mL/min [12]. There are not enough data to establish a recommendation for dose adjustment in patients with CL_{CR} < 30 mL/min. Dialysis was effective in completely removing eslicarbazepine acetate metabolites from circulation [12].

To asses the role of liver function on eslicarbazepine acetate conversion to eslicarbazepine and on the glucuronidation of eslicarbazepine and minor primary metabolites, eslicarbazepine acetate pharmacokinetics was evaluated following multiple dosing (800 mg once daily for 8 days) to patients with moderate liver impairment (Child–Pugh score of 7–9, n = 8) and to healthy subjects (n = 8) who served as a control group [7]. Eslicarbazepine acetate pharmacokinetics was not affected by moderate hepatic impairment. Although there were more subjects with measurable

plasma eslicarbazepine acetate concentrations in the hepatic impairment group than in the control group, plasma eslicarbazepine acetate concentrations remained very low (<0.1% of eslicarbazepine concentrations). No significant differences were found in eslicarbazepine acetate and eslicarbazepine concentration–time profiles in patients with and without portal-systemic shunting, suggesting that eslicarbazepine acetate hydrolysis to eslicarbazepine during first passage is not affected by portal-systemic shunting [7]. In addition, there were no significant differences between liver-impaired and control patients in the pharmacokinetics of the glucuronide metabolites, and the relative proportion of other minor metabolites remained unchanged. Thus, moderate liver impairment has no relevant effect on glucuronidation or on the formation of (*R*)-licarbazepine and oxcarbazepine [7]. No data are available for patients with severe liver impairment.

Drug interactions

Effect of other drugs on eslicarbazepine acetate pharmacokinetics

Eslicarbazepine acetate metabolism was not inhibited by incubating [^{14}C]eslicarbazepine acetate with the AEDs acetazolamide, clobazam, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone or valproic acid [17]. In a population pharmacokinetic analysis in patients with epilepsy, eslicarbazepine CL/*F* was found to be increased in patients treated with inducing AEDs (carbamazepine, phenobarbital and phenytoin). Lamotrigine, valproic acid, topiramate, gabapentin, clobazam and levetiracetam did not affect eslicarbazepine exposure [13].

Effect of other drugs on eslicarbazepine acetate pharmacokinetics

In human liver microsomes, eslicarbazepine appeared to have a minimal or no inhibitory effect on the activity of the cytochrome P450 (CYP) enzymes CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1, CYP3A4 and CYP4A9/11 as well as on uridine diphosphate-5′-glucuronosyltransferases (UGTs) UGT1A1 and UGT1A6, and epoxide hydrolase (EH) [29]. A moderate inhibitory effect was found on CYP2C9-mediated tolbutamide 4-hydroxylation, and IC_{50} values for eslicarbazepine on CYP2C19 activity (utilizing tolbutamide as a CYP2C19 probe) were 232 μg/mL. Studies with eslicarbazepine in fresh human hepatocytes showed no induction of CYP1A2, CYP3A4 and phase II hepatic enzymes involved in glucuronidation and sulphation [29].

Population pharmacokinetic analyses in patients with epilepsy showed that eslicarbazepine acetate did not influence to a clinically relevant extent the CL/*F* of carbamazepine, levetiracetam, valproic acid, clobazam, gabapentin or phenobarbital [13]. An increase in plasma phenytoin concentrations was observed following short-term co-administration of eslicarbazepine acetate (1200 mg once daily) and a controlled-release phenytoin formulation (300 mg once daily) to healthy subjects, which could be explained by inhibition of CYP2C9 and CYP2C19. However, no relevant effect of eslicarbazepine acetate on plasma phenytoin levels was seen in the analysis of patients with epilepsy [13]. Although both eslicarbazepine acetate metabolites and lamotrigine undergo glucuronidation, studies in healthy subjects [30] and in patients with epilepsy [13] showed no clinically relevant effect of eslicarbazepine acetate on lamotrigine pharmacokinetics. Eslicarbazepine acetate (1200 mg once daily) caused a small decrease in topiramate systemic exposure in healthy subjects, but no relevant changes occurred on trough plasma concentrations of concomitant AEDs in patients administered eslicarbazepine acetate maintenance doses of 400 mg and 800 mg once daily. Overall, the magnitude of concomitant eslicarbazepine acetate effects on the plasma levels of all concomitant AEDs assessed appears not to be clinically relevant and would not require dose adjustment of any of the above AEDs.

Co-administration of eslicarbazepine acetate (1200 mg once daily for 8 days) with warfarin showed a mild but significant decrease in *S*-warfarin exposure, with no significant effect on *R*-warfarin pharmacokinetics or on coagulation [international normalized ratio (INR)] [31]. A study in healthy subjects showed no effect of eslicarbazepine acetate 1200 mg once daily on digoxin pharmacokinetics [32].

Administration of eslicarbazepine acetate 1200 mg once daily to women decreased the systemic exposure to levonorgestrel and ethinylestradiol from a combined oral contraceptive, which was most likely caused by induction of CYP3A4 [13]. Thus, concurrent use of eslicarbazepine acetate and oral contraceptives may result in decreased contraceptive effectiveness.

Serum level monitoring and pharmacokinetic/pharmacodynamic relationships

A pharmacokinetic/pharmacodynamic analysis in the pooled population of eslicarbazepine acetate phase III studies in patients with epilepsy was performed using non-linear mixed-effect modelling (NONMEM) [13]. Efficacy variables derived from the seizure frequency standardized for 4 weeks were best fitted by a combination of a baseline, a placebo effect and an effect of eslicarbazepine acetate described by an E_{max} pharmacodynamic model. The antiepileptic effect of eslicarbazepine acetate, as assessed by seizure frequency, increased with the increase of eslicarbazepine acetate dose. Concomitant administration of other AEDs did not affect eslicarbazepine exposure–response relationships, although carbamazepine and phenobarbital did decrease eslicarbazepine plasma exposure (AUC). Overall, the results of this analysis demonstrated a continuous relationship, with moderate inter-subject variability, between antiepileptic efficacy and eslicarbazepine concentrations or plasma exposure that was not affected by concomitant AEDs.

The above analysis, however, does not provide sufficient information on the value of monitoring serum eslicarbazepine levels. A reference serum eslicarbazepine concentration in patients receiving eslicarbazepine acetate therapy has not yet been clearly established.

Efficacy

Efficacy in placebo-controlled clinical trials

Evidence of efficacy of eslicarbazepine acetate as adjunctive therapy in adults with partial-onset seizures with or without sec-

ondary generalization was obtained in a phase II study and three phase III studies.

The phase II study was a multicentre, double-blind, randomized, placebo-controlled study conducted in 143 refractory patients aged between 18 and 65 years with four or more partial-onset seizures per month, despite treatment with one or two AEDs [33]. Carbamazepine and oxcarbazepine were not allowed as concomitant AEDs. The study consisted of a retrospective 2-month baseline followed by a prospective 12-week treatment period and a 1-week tapering off. Patients were randomly assigned to one of three treatment groups: eslicarbazepine acetate once daily ($n = 50$), eslicarbazepine acetate twice daily ($n = 46$) or placebo ($n = 47$). The daily dose was titrated from 400 mg to 800 mg and to 1200 mg at 4-week intervals. After 12 weeks of treatment, the proportion of responders (patients with a ≥50% seizure reduction) in the intention-to-treat (ITT) population (primary efficacy analysis) was 54% with eslicarbazepine acetate once daily, 41% with eslicarbazepine acetate twice daily and 28% with placebo. The difference compared with placebo was statistically significant for the once-daily group only ($P < 0.01$). The results suggested that an eslicarbazepine acetate once-daily regimen was as efficacious as (or possibly more efficacious than) the same daily dose given in a twice-daily regimen, and the once-daily regimen was therefore adopted in phase III studies. The once-daily dosing allows higher peak plasma concentration of the eslicarbazepine acetate active entity eslicarbazepine than the twice-daily dosing of the same daily dose, which suggests that efficacy following eslicarbazepine acetate once-daily treatment correlates better with the peak plasma concentration at steady state (a parameter that reflects extent and rate of absorption) than with AUC_{ss} (a parameter that reflects only extent of absorption) [33].

The phase III programme consisted of three pivotal, multicentre, double-blind, randomized, placebo-controlled studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303) in 1049 adult refractory patients enrolled by 125 sites in 23 countries. The studies consisted of an 8-week baseline period, a 2-week titration period (no titration in the 400-mg and 800-mg arms of study BIA-2093-302), a 12-week maintenance period, and a 4-week tapering-off period (only in studies BIA-2093-301 and BIA-2093-303). At randomization, patients were meant to have four or more partial-onset seizures per 4 weeks during the baseline period, despite treatment with one or two concomitant AEDs in studies BIA-2093-301 and BIA-2093-303, and one to three AEDs in study BIA-2093-302. All marketed AEDs, except oxcarbazepine and felbamate, were allowed as concomitant AEDs.

In the phase III pooled population [13], 81% of patients were white, mean age was 37 years (range 17–77 years) and mean epilepsy duration was 22 years (range 1–71 years). In study BIA-2093-301, 468 patients enrolled in the baseline period and 402 (86%) were randomized to treatment. In study BIA-2093-302, 503 enrolled and 395 (79%) were randomized, and in study BIA-2093-303, 330 enrolled and 253 (77%) were randomized. After carbamazepine (approximately 60% of all patients enrolled), the most commonly used concomitant AEDs were valproic acid, lamotrigine, levetiracetam, topiramate, phenytoin, phenobarbital and clobazam, which were taken by up to 30% of patients in any treatment group. Between 64% and 75% of patients received two concomitant AEDs. The key efficacy endpoints were seizure frequency standardized per 4 weeks (primary analysis in all studies), median relative reduction in standardized seizure frequency, and responder rate (proportion of patients with at least 50% reduction in standardized seizure compared with baseline). The prespecified (a priori) primary efficacy analysis was conducted on the natural log transformation of the standardized seizure frequency.

Standardized seizure frequency over the 12-week maintenance period in the individual studies is shown in Figure 38.6. Standardized seizure frequency was compared between each active treatment group and the placebo group using an analysis of covariance (ANCOVA) that modelled seizure frequency as a function of baseline seizure frequency and treatment. In the pooled population, standardized seizure frequency during the maintenance period was significantly different from placebo with eslicarbazepine acetate 800 mg and 1200 mg once daily, in both the ITT and per-protocol (PP) analysis. In the PP population, the difference between the eslicarbazepine acetate 400 mg and placebo group was also statistically significant. The responder rate was also higher in the eslicarbazepine acetate 800 mg and 1200 mg groups than in the placebo group in the ITT population and the PP population (Table 38.2). Relative reduction in standardized seizure frequency during the maintenance period was statistically significant for the 800 mg and 1200 mg eslicarbazepine acetate groups compared with placebo (Table 38.3). Analyses performed on each of the three key efficacy endpoints to demonstrate the robustness of the findings were consistent with the results shown for the models used above.

Analyses of the secondary efficacy variables showed a level of efficacy in the 800 mg and 1200 mg eslicarbazepine acetate groups consistent with that observed for the key efficacy variables. The response to treatment was evident already in the first week of the titration period and reached its peak in the first week of the maintenance period. The responder rate was 46% in the eslicarbazepine acetate 800 mg group and 53% in the eslicarbazepine acetate 1200 mg group in the first week of the maintenance period, and remained stable through the last week of the maintenance period. During the maintenance period, the median number of days with seizures per 4 weeks decreased only from 5.9 to 5.3 in the placebo group, but from 6.5 at baseline to 4.3 in the 800 mg eslicarbazepine acetate group ($P = 0.0054$ versus placebo) and from 6.3 to 3.8 in the 1200 mg group ($P = 0.0007$). The proportion of patients who completed the study and were seizure free during the maintenance phase (expressed as a percentage of those who reached the maintenance phase) increased with increasing eslicarbazepine acetate dose, from 2% of eslicarbazepine acetate 400 mg patients and 3% of placebo patients, to 4% of eslicarbazepine acetate 800 mg patients and 8% of eslicarbazepine acetate 1200 mg patients. During the tapering-off period (studies BIA-2093-301 and BIA-2093-303 only), the standardized seizure frequency remained essentially constant in the placebo group relative to the end of the maintenance period and increased slightly in the eslicarbazepine acetate groups without any sign of a rebound effect. The efficacy of eslicarbazepine acetate was not altered when given concomitantly with carbamazepine (pre-dose plasma concentrations of 6.9 ± 2.6 mg/L), lamotrigine (4.3 ± 2.8 mg/L) or valproic acid (54.8 ± 31.1 mg/L), the most widely used concomitant AEDs. The median decrease in seizure frequency was similar in patients not taking carbamazepine (placebo, 15%; 400 mg, 24%; 800 mg, 39%; 1200 mg, 38%) and those taking carbamazepine (placebo, 14%; 400 mg, 23%; 800 mg, 33%; 1200 mg, 44%).

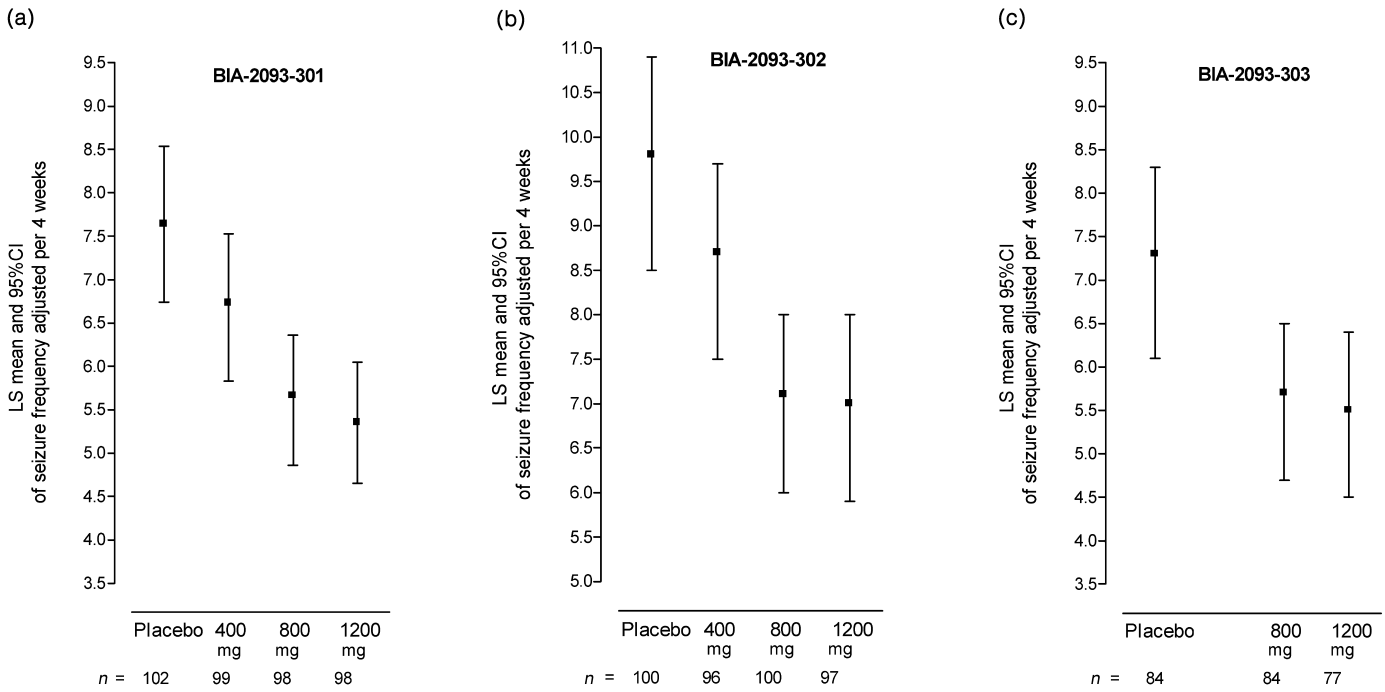

Fig. 38.6 Standardized seizure frequency over the 12-week maintenance period in the eslicarbazepine acetate phase III studies (intent-to-treat population). LS, least square.

Table 38.2 Responder rate in the pooled population of phase III studies with eslicarbazepine acetate as adjunctive therapy in patients with partial epilepsy. Responder rates were calculated over the maintenance period.

Treatment	*n*	Number (%) of responders	Odds ratio		Relative risk		*P*-value[a]
			Estimate	95% CI	Estimate	95% CI	
ITT population							
Placebo	279	60 (21.5)	–	–	–	–	–
Eslicarbazepine acetate 400 mg	192	44 (22.9)	1.25	0.77–2.04	1.19	0.81–1.76	n.s.
Eslicarbazepine acetate 800 mg	262	95 (36.3)	2.08	1.42–3.04	1.69	1.28–2.22	<0.001
Eslicarbazepine acetate 1200 mg	253	110 (43.5)	2.81	1.92–4.10	2.02	1.55–2.63	<0.0001
PP population							
Placebo	223	45 (20.2)	–	–	–	–	–
Eslicarbazepine acetate 400 mg	164	40 (24.4)	1.46	0.86–2.48	1.35	0.89–2.05	n.s.
Eslicarbazepine acetate 800 mg	208	75 (36.1)	2.22	1.44–3.41	1.79	1.30–2.46	<0.001
Eslicarbazepine acetate 1200 mg	161	75 (46.6)	3.44	2.19–5.40	2.31	1.69–3.14	<0.0001

CI, confidence interval; ITT, intent-to-treat; n.s., not statistically significant; PP, per-protocol.
[a] Chi-square test.

Long-term benefit in open-label extensions of phase III studies

Of the 857 patients who completed the double-blind phase of studies BIA-2093-301, BIA-2093-302 and BIA-2093-303, 833 (97%) entered long-term treatment with eslicarbazepine acetate (extension phase) and 612 (73.5%) patients completed 1 year of treatment [13]. Investigators could titrate eslicarbazepine acetate dosage according to clinical response. In all studies, the mean daily dose was approximately 900 mg (median, 800 mg), and this was stable throughout the 1-year follow-up period. The last observation carried forward method was used in the ITT efficacy analyses. The decrease in seizure frequency relative to baseline was sustained over the 1-year treatment period. In study BIA-2093-301, median seizure frequency during the first 4 weeks of the extension phase was 39% lower than during baseline and continued to decrease, being reduced (compared with baseline) by 48% in weeks 5–16 and 56% in weeks 41–52. Responder rate during weeks 1–4 was 41% and continued to increase over time, from 48% in weeks 5–16 to 53% in weeks 41–52. The proportion of seizure-free patients per 12-week interval increased over time, ranging from 9% of patients during weeks 5–16 to 13% during weeks 41–52. In study BIA-2093-302, median seizure frequency decreased by 32% in weeks 1–4 and by 38% in weeks 5–16 to 39% in weeks 41–52; responder rate was 37% during

the first 4 weeks and thereafter ranged between 38% and 42%. The proportion of seizure-free patients per 12-week interval increased from 5% in weeks 5–16 to 11% in weeks 41–52%. In study BIA-2093-303, median seizure frequency was reduced by 48% in weeks 1–4 and by between 54% and 58% in the remaining treatment period. The responder rate was 46% in weeks 1–4 and thereafter ranged between 53% and 56%. The proportion of seizure-free patients per 12-week interval increased over time, from 6% (weeks 5–16) to 18% (weeks 41–52).

Quality of life was assessed using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) questionnaire, and depressive symptoms were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS). Statistically significant improvements (last assessment versus baseline) were found in the health-related outcomes for both these questionnaires in all the open-label extensions to the phase III studies.

Table 38.3 ANCOVA of relative reduction (%) in standardized seizure frequency in the pooled population of phase III studies with eslicarbazepine acetate as adjunctive therapy in patients with partial epilepsy. Standardized seizure frequencies were calculated over the maintenance period.

Treatment	*n*	LS mean (%)	SE	95% CI	*P*-value
ITT population					
Placebo	278	–8.5	5.30	(–18.9 to 1.9)	–
Eslicarbazepine acetate 400 mg	192	–17.7	6.22	(–29.9 to –5.4)	n.s.
Eslicarbazepine acetate 800 mg	262	–29.4	5.32	(–39.8 to –19.0)	0.0002
Eslicarbazepine acetate 1200 mg	251	–30.6	5.43	(–41.3 to –20.0)	<0.0001
PP population					
Placebo	223	–14.6	4.90	(–24.1 to –5.0)	–
Eslicarbazepine acetate 400 mg	164	–23.6	5.68	(–34.8 to –12.5)	<0.05
Eslicarbazepine acetate 800 mg	208	–33.1	4.92	(–42.7 to –23.4)	<0.0001
Eslicarbazepine acetate 1200 mg	161	–41.7	5.38	(–52.2 to –31.1)	<0.0001

ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; LS, least square; n.s., not statistically significant; PP, per-protocol; SE, standard error. Results are based on an ANCOVA model with treatment, study, baseline seizure frequency and number of concomitant antiepileptic drugs at baseline as factors. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

Adverse effects

To date, more than 2500 subjects have received eslicarbazepine acetate in completed or ongoing phase I to phase III studies.

Adverse events in adults with epilepsy

In the phase II study [33], the percentage of patients reporting treatment-emergent adverse events (AEs) was similar in the three treatment groups: 38.0% in the 400–1200 mg once daily group, 41.3% in the 200–600 mg twice daily group and 44.7% in the placebo group. Most of the AEs (68.3%) were of mild intensity. The most frequent were headache, dizziness and nausea. AEs leading to discontinuation occurred in a similar proportion in patients treated with placebo (10.6%) and eslicarbazepine acetate (9.4%).

In the double-blind phase of the integrated phase III studies there was a dose-dependent increase in AEs with increasing dose of eslicarbazepine acetate (Table 38.4) [13]. This was also observed for possibly related AEs and AEs leading to discontinuation. AEs occurred mainly during the first weeks of treatment; no difference was found between eslicarbazepine acetate and placebo in incidence of AEs after 6 weeks of treatment. In the 1-year open-label extension of study BIA-2093-301, 50.3% of patients reported AEs, 26.8% reported possibly related AEs, 6.2% reported serious AEs and 4.5% reported AEs leading to discontinuation. The majority of AEs in either the double-blind phase of the integrated phase III population or the extension phase of study BIA-2093-301 were reported by <3% of patients in any treatment group (Table 38.5). The most common AEs, in both the placebo and combined eslicarbazepine acetate groups were dizziness, somnolence, headache and nausea.

Hyponatraemia <125 mmol/L was recorded in only four patients: one (0.5%) on eslicarbazepine acetate 400 mg, two (0.7%) on eslicarbazepine acetate 800 mg and one (0.4%) on eslicarbazepine acetate 1200 mg. Hypernatraemia (>146 mmol/L) was recorded in one (0.3%) patient on placebo, one (0.5%) on eslicarbazepine acetate 400 mg and one (0.4%) on eslicarbazepine acetate 800 mg. The incidence of rash was also low and dose dependent: one (0.3%) patient on placebo, one (0.5%) on eslicarbazepine acetate 400 mg, three (1.1%) on eslicarbazepine acetate 800 mg and nine (3.2%) on eslicarbazepine acetate 1200 mg. The majority of patients in the eslicarbazepine acetate

Table 38.4 Summary of treatment-emergent adverse events (AEs) in the pooled population of phase III studies with eslicarbazepine acetate as adjunctive therapy in patients with partial epilepsy.

Type of AE	Number (%) of patients			
	Placebo (*n* = 289)	Eslicarbazepine acetate 400 mg (*n* = 196)	Eslicarbazepine acetate 800 mg (*n* = 284)	Eslicarbazepine acetate 1200 mg (*n* = 280)
All AEs	134 (46.4)	119 (60.7)	178 (62.7)	189 (67.5)
Possibly related AEs	72 (24.9)	75 (38.3)	134 (47.2)	154 (55.0)
Serious AEs	4 (1.4)	9 (4.6)	10 (3.5)	9 (3.2)
AEs leading to discontinuation	13 (4.5)	17 (8.7)	33 (11.6)	54 (19.3)

Table 38.5 Treatment-emergent adverse events (AEs) in > 3% in any treatment group, by decreasing frequency, in the pooled population of phase III studies with eslicarbazepine acetate as adjunctive therapy in patients with partial epilepsy.

AE preferred term (MedDRA dictionary)	Number (%) of patients				
	Integrated phase III studies, double-blind phase				Study 301 extension phase[a]
	Placebo (*n* = 289)	Eslicarbazepine acetate 400 mg (*n* = 196)	Eslicarbazepine acetate 800 mg (*n* = 284)	Eslicarbazepine acetate 1200 mg (*n* = 280)	Total eslicarbazepine acetate (*n* = 314)
Total patients with AEs	*134 (46.4)*	*119 (60.7)*	*178 (62.7)*	*189 (67.5)*	*158 (50.3)*
Dizziness	21 (7.3)	26 (13.3)	60 (21.1)	81 (28.9)	30 (9.6)
Somnolence	27 (9.3)	21 (10.7)	37 (13.0)	42 (15.0)	11 (3.5)
Headache	25 (8.7)	17 (8.7)	29 (10.2)	38 (13.6)	32 (10.2)
Nausea	6 (2.1)	10 (5.1)	21 (7.4)	28 (10.0)	9 (2.9)
Diplopia	5 (1.7)	10 (5.1)	23 (8.1)	24 (8.6)	17 (5.4)
Vomiting	7 (2.4)	4 (2.0)	19 (6.7)	20 (7.1)	4 (1.3)
Coordination abnormal	6 (2.1)	6 (3.1)	15 (5.3)	17 (6.1)	1 (0.3)
Vision blurred	3 (1.0)	8 (4.1)	11 (3.9)	11 (3.9)	3 (1.0)
Influenza	6 (2.1)	7 (3.6)	6 (2.1)	8 (2.9)	5 (1.6)
Vertigo	1 (0.3)	4 (2.0)	5 (1.8)	11 (3.9)	12 (3.8)
Diarrhoea	3 (1.0)	2 (1.0)	12 (4.2)	6 (2.1)	2 (0.6)
Fatigue	8 (2.8)	4 (2.0)	5 (1.8)	9 (3.2)	0
Constipation	3 (1.0)	6 (3.1)	3 (1.1)	6 (2.1)	2 (0.6)
Rash	1 (0.3)	1 (0.5)	3 (1.1)	9 (3.2)	3 (1.0)
Depression	1 (0.3)	6 (3.1)	2 (0.7)	5 (1.8)	1 (0.3)
Nasopharyngitis	8 (2.8)	6 (3.1)	2 (0.7)	4 (1.4)	16 (5.1)
Abdominal pain upper	9 (3.1)	3 (1.5)	3 (1.1)	4 (1.4)	5 (1.6)

[a] 1-year open-label extension.

(84.8%) and placebo (90.3%) treatment groups had AEs of mild or moderate intensity. While the overall frequency of mild AEs was similar in all treatment groups, the frequency of moderate and severe events was highest in the eslicarbazepine acetate 1200 mg group. With respect to nervous system AEs, 4.6% of 800 mg eslicarbazepine acetate patients, compared with 8.2% of 1200 mg patients, reported severe AEs. However, this difference cannot be attributed to any single type of event, with the exception of dizziness, which was reported as severe by 4.3% of patients in the eslicarbazepine acetate 1200 mg group compared with 2.1% of patients in the 800 mg group.

The incidence of patients reporting AEs was related to the starting dose in the integrated phase III studies. From the start of treatment to 4 weeks after the titration period, AEs were reported by 33.2% of patients in the placebo group, 44.9% in the 400 mg group and between 35% and 45% in all titration regimens that started at 400 mg and increased to 800 mg or 1200 mg. In contrast, the frequency of AEs in this time frame was 51.3% in patients who began treatment at 600 mg and 73.3% to 77.6% in patients who began at 800 mg.

The proportion of patients with AEs leading to treatment discontinuation was highest in the eslicarbazepine acetate 1200 mg group (19.3%) and lowest in the placebo group (4.5%). The increased incidence of patients discontinuing in the eslicarbazepine acetate groups was primarily due to vertigo, diplopia, blurred vision, nausea and vomiting, fatigue, abnormal coordination, dizziness, headache and somnolence. The overall incidence of serious AEs was low in all treatment groups (<5% of patients). The most common serious AEs (more than two patients in any group) were abnormal coordination, vomiting, drug toxicity (a mEDRA term that includes several types of symptoms reported by the investigators that can be a sign of toxicity/intoxication), diplopia and grand mal convulsion, none of which were reported in placebo-treated patients.

In placebo-treated patients, the incidence of AEs was 50% in patients receiving concomitant carbamazepine versus 40% in patients not receiving carbamazepine. In the eslicarbazepine acetate groups, the incidence of AEs in patients receiving concomitant carbamazepine treatment was 68–73% versus 51–61% in patients receiving eslicarbazepine acetate without carbamazepine. The observation that in both the eslicarbazepine acetate and the placebo groups the incidence of AEs was higher in patients co-medicated with carbamazepine suggests that concomitant treatment of eslicarbazepine acetate and carbamazepine appears not to result in a supra-additive effect on the incidence of AEs.

Adverse events in children with epilepsy

In a phase IIa study of 31 children [28], eslicarbazepine acetate 5 mg/kg/day and 15 mg/kg/day dose regimens were well tolerated. All drug-related AEs reported at these doses were mild in intensity, except for one case of psychomotor agitation of moderate intensity with the lowest dose. At the dosage of 30 mg/kg/day, AEs were more frequent, tended to be more severe and were mainly related to the nervous system. The AE profile in children was in line with that observed in adults.

Adverse events in healthy subjects

To date, eslicarbazepine acetate has been administered to more than 700 healthy subjects in phase I studies. The most common AEs reported with eslicarbazepine acetate treatment in these sub-

jects included headache, somnolence/tiredness, dizziness, and paraesthesia affecting the mouth, lips or tongue; in addition, nausea, vomiting and upper respiratory tract infection/inflammation were reported in some studies. In general, the observed AEs were mild to moderate in severity, limited in duration and manageable. The maximum tolerated eslicarbazepine acetate dose in healthy subjects was established to be 2400 mg once daily, with eslicarbazepine acetate treatment starting without titration [13].

Other safety parameters

There were no clinically significant changes, no dose- or age-dependent patterns, and no clinically relevant individual abnormalities in laboratory parameters, vital signs or physical examinations in the phase I, phase II or phase III studies [13]. There were also no safety concerns from the electrocardiogram (ECG) parameters assessed from 12-lead ECGs. In a moxifloxacin-controlled thorough QT/QTc study in healthy subjects, eslicarbazepine acetate 1200 and 2400 mg once daily showed no effect on ECG intervals or morphology [13].

Place in current therapy

Despite a broad range of AEDs currently available, about 30% of patients with epilepsy are uncontrolled with available treatments and a further 25% suffer from manifestations of drug toxicity. Eslicarbazepine acetate is a novel AED chemically related to carbamazepine and oxcarbazepine that mainly undergoes metabolic hydrolysis followed by glucuronidation with minimal CYP-mediated metabolism.

The phase III studies allowed the inclusion of patients who were concomitantly taking carbamazepine. Although carbamazepine and eslicarbazepine acetate are chemically related, they do not share any common metabolite(s). Therefore, it was considered justified not to exclude carbamazepine-treated patients from eslicarbazepine acetate phase II and III trials. Indeed, when the efficacy of eslicarbazepine acetate in relation to the most common co-medications in the phase III study (carbamazepine, lamotrigine and valproic acid) was assessed, it was found that the degree of improvement on eslicarbazepine acetate was the same, irrespective of the type of concomitant AEDs.

One question that needs to be considered is why eslicarbazepine acetate should be used as an adjunctive therapy with other sodium channel-blocking AEDs, such as carbamazepine, lamotrigine or phenytoin, at therapeutic doses, and why we see additive efficacy when eslicarbazepine acetate is used together with these AEDs. The answer to this must include consideration of several factors, including aspects such as additional mechanisms of action of individual AEDs different from sodium channel blockade and the biopharmaceutical properties and pharmacokinetic profile of the eslicarbazepine acetate active entity eslicarbazepine. It has been postulated that one reason for pharmacoresistance is that voltage-gated sodium channels in resistant patients are altered in their protein subunits so that their sensitivity to AEDs is diminished [34]. It is possible that, in such patients, voltage-gated sodium channels are more responsive to a specific sodium channel blocker than to another. Thus, it may be possible to elicit a stronger response by providing adjunctive therapy with a different sodium channel blocker. Furthermore, regulation of seizure-induced transcriptional plasticity differs in different neuron types [35,36] and may make some channel proteins more responsive to one sodium channel-blocking AED over another. Post-transcriptional modifications of ion channel proteins due to seizures, such as changes in the degree of phosphorylation, have been shown to alter the sensitivity of the channel proteins to AEDs. For example, increased phosphorylation of a channel protein changed the responsiveness of that protein to topiramate [37]. There is also previous evidence demonstrating the additive efficacy from combining different sodium channel blockers, even though in the case of the oxcarbazepine–carbamazepine combination this may be associated with relatively high intolerability rates [38]. There are thus both mechanistic concepts and empirical experience that substantiate the use of eslicarbazepine acetate as adjunctive therapy with other sodium channel-blocking AEDs.

Although neurological and psychiatric events are known side-effects of AEDs, the incidence of psychiatric events was low (<1%) with eslicarbazepine acetate. The neurological AEs – somnolence, dizziness, headache and abnormal coordination – had a dose-dependent incidence with eslicarbazepine acetate treatment, but in the integrated phase III population, none of the neurological events were reported by >15% of patients in any eslicarbazepine acetate treatment groups. In studies of similar design and duration, neurological events were reported by between 8% and 43% of patients treated with prebagalin 600 mg/day [39] and by between 5% and 16% of patients treated with levetiracetam 1000–2000 mg/day [40], which are two of the more recent and widely used AEDs. Thus, although one has to be cautious in making comparisons across trials, eslicarbazepine acetate offers a similar or lower risk of experiencing the neurological and psychiatric events commonly associated with AED treatment.

In conclusion, the favourable efficacy and safety profiles of eslicarbazepine acetate 800 and 1200 mg, including the sustained efficacy for at least 1 year and the lack of major concerns related to rash, hyponatraemia or body weight increase, indicate that eslicarbazepine acetate is a valuable addition to the current armamentarium of AEDs as an adjunctive therapy for refractory partial-onset seizures. Eslicarbazepine acetate has not been assessed in generalized epilepsies, but, based on its structural and mechanistic similarities with carbamazepine and oxcarbazepine, it may be expected to be potentially aggravating on some primary generalized seizure types, particularly myoclonic and absence seizures.

With its once-daily dosing and simple titration regimen, eslicarbazepine acetate offers a more favourable dosing regimen compared with many of the currently available AEDs, which are dosed several times a day and involve complex and long-term titration schemes. The use of eslicarbazepine acetate will no doubt increase in the future, and the resulting clinical experience will be crucial to define its place in the treatment algorithm.

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39 Ethosuximide

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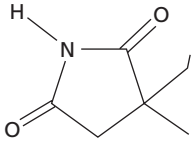

Primary indications	First-line or adjunctive therapy of generalized absence seizures; also helpful in absence status epilepticus and in some generalized epilepsies in childhood, particularly those associated with absence or myoclonic seizures
Usual preparations	Capsules: 250 mg; syrup: 250 mg/5 mL
Usual dosages	Initial: 250 mg (adults); 10–15 mg/kg/day (children). Maintenance: 750–1500 mg/day (adults); 15–40 mg/kg/day (children)
Dosing frequency	2–3 times/day
Significant drug interactions	Ethosuximide levels are reduced by co-medication with carbamazepine, phenytoin, phenobarbital and rifampicin. Valproic acid may exert synergistic effects with ethosuximide in patients refractory to either drug given alone, and may have variable and inconsistent effects on ethosuximide levels. Serum valproic acid levels may be decreased by ethosuximide. Ethosuximide levels are increased by isoniazid
Serum level monitoring	Ethosuximide therapy is usually optimized based on clinical and EEG response. Monitoring serum ethosuximide levels, however, may be useful in selected cases
Reference range	40–100 mg/L
Common/important adverse effects	Gastrointestinal symptoms, drowsiness, ataxia, diplopia, headache, dizziness, hiccoughs, sedation, behavioural disturbances, acute psychotic reactions, extrapyramidal symptoms, blood dyscrasias, rash, lupus-like syndrome, other severe idiosyncratic reactions
Main advantages	Well-established treatment for absence epilepsy without the risk of hepatic toxicity carried by valproic acid
Main disadvantages	Adverse effects common. Unlike valproic acid, ethosuximide does not protect against generalized tonic–clonic seizures
Mechanisms of action	Inhibition of neuronal T-type calcium channels. Other actions may contribute to clinical effects
Oral bioavailability	90–100%
Time to peak levels	Usually within 1–5 h
Elimination	Primarily by oxidation, largely catalysed by cytochrome CYP3A4
Volume of distribution	0.6–0.7 L/kg
Elimination half-life	25–70 h (shortest values in children and in subjects co-medicated with enzyme inducers)
Plasma clearance	7–20 mL/kg/h (highest values in children and in subjects co-medicated with enzyme inducers)
Protein binding	<10%
Active metabolites	None
Comment	Ethosuximide is an alternative to valproic acid as a treatment of first choice in childhood absence epilepsy. It is useful in other syndromes associated with absence and/or myoclonic seizures

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Introduction

Ethosuximide was introduced in the 1950s as an effective and relatively well-tolerated drug for the treatment of absence seizures. Trimethadione and its analogue paramethadione, introduced in the 1940s, were the first agents that had demonstrated efficacy against absence seizures, but were associated with significant toxicity [1]. These toxicity issues prompted the discovery and testing in the 1950s of different members of the succinimide family (ethosuximide, methsuximide and phensuximide), and ethosuximide showed the greatest efficacy against absence seizures and the least toxicity [2]. Ethosuximide has been considered as a first-line therapy for absence seizures since its introduction in 1958 [3].

Chemistry

Ethosuximide (2-ethyl-2-methylsuccinimide, molecular weight 141.2) is a chiral molecule containing a five-member ring, two negatively charged carbonyl oxygen atoms with a ring nitrogen between them and one asymmetric carbon atom.

It has a melting point of 64–65°C, along with a weakly acidic p*K*a of 9.3, and a partition coefficient of 9 (chloroform/water; pH 7). Ethosuximide is freely soluble in ethanol and water (solubility 190 mg/mL) [4]. A white crystalline material, ethosuximide is used clinically as a racemate and is commercially available in 250-mg capsules or 250 mg/5 mL syrup.

Pharmacology

Activity in experimental models of seizures and epilepsy

Ethosuximide blocks clonic seizures produced by subcutaneously administered pentylenetetrazole or bicuculline, but it is ineffective against maximal electroshock-induced tonic seizures, except at anaesthetic doses [5]. Likewise, ethosuximide is ineffective against kindled seizures or the evolution of the kindling process, except for some weak activity at neurotoxic concentrations [5,6]. This activity profile suggests that ethosuximide exerts its anticonvulsant effects by raising seizure threshold rather than by blocking the spread of seizures, and predicts efficacy against absence rather than partial-onset and generalized tonic–clonic seizures [7]. Ethosuximide's major metabolite, 2-(1-hydroxyethyl)-2-methylsuccinimide, demonstrated no significant activity against pentylenetetrazole-induced clonic seizures in mice [8].

Ethosuximide demonstrates activity against spontaneously occurring absence seizures in various animal models, including the mutant tottering mouse, the Genetic Absence Epilepsy Rat from Strasbourg and the double-mutant spontaneously epileptic rat [9–11]. It also demonstrates activity against spike–wave seizures induced by systemic administration of γ-hydroxybutyrate in rodents and primates [7,12–14], and against fuorothyl-induced clonic convulsions in Mongolian gerbils [15]. Pretreatment with ethosuximide has been found to attenuate in a dose-dependent manner non-convulsive seizures induced by brain ischaemia [16].

Activity in experimental models relevant to other indications

Recent studies have shown that ethosuximide shows analgesic activity in various nociceptive pain models. Models in which activity has been demonstrated include chemotherapy-induced peripheral neuropathic pain, capsaicin-induced mechanical hyperalgesia, the rat-tail flick reflex test, the formalin model of persistent pain and acute peripheral thermal nociception in rats [5].

Mechanisms of action

Ethosuximide's presumed mechanism of action against absence seizures is reduction of low-threshold T-type calcium currents in thalamic neurones [17,18], though actions at cortical level may also be important [19].

The spontaneous pacemaker oscillatory activity of thalamocortical neurones involves low-threshold T-type calcium currents [20]. These oscillatory currents are considered to be the generators of the 3-Hz spike-and-wave rhythms noted in patients with absence epilepsy [20]. Voltage-dependent blockade of the low-threshold T-type calcium current was demonstrated at clinically relevant ethosuximide concentrations in thalamic neurones isolated from rats and guinea pigs [17,18,20]. Gating of these T-type calcium channels is not altered by ethosuximide [2,18]. Based on these findings, it is proposed that ethosuximide's effect on low-threshold T-type calcium currents in thalamocortical neurones prevents the synchronized firing associated with spike–wave discharges [17]. Likewise, an action on T-type calcium channels in sensory neurones has been proposed as the main mechanism responsible for the effects of ethosuximide in models of neuropathic pain [5].

In recent years, evidence has been presented that additional mechanisms beyond blockade of T-type calcium channels may contribute to the actions of ethosuximide [5]. These include a reduction in persistent sodium- and calcium-activated potassium currents in thalamic and layer V cortical pyramidal neurones, a reduction in cortical γ-aminobutyric acid (GABA) levels and, possibly, a decrease in pathologically increased glutamate levels in the motor cortex [5].

Pharmacokinetics

Ethosuximide shows linear pharmacokinetics. The drug is used as a racemate, but in most pharmacokinetic studies no differentiation was made between the two enantiomers. In a study conducted in 33 patients on chronic ethosuximide treatment, the ratio between the enantiomers in plasma was close to unity, indicating that the disposition of the drug in humans is non-stereoselective and that measurement of total ethosuximide levels for therapeutic monitoring is reasonable and appropriate [4,21]. The non-stereoselective disposition of ethosuximide was unaffected by pregnancy, placental transfer or passage into breast milk in a small study (three pregnancies in two women taking ethosuximide) [22].

Absorption

Although there is no intravenous formulation that can be used as a reference standard to determine absolute bioavailability in humans, the absorption of ethosuximide is considered to be rapid

and nearly complete (90–100%) in children and adults [3,23–25]. Peak plasma concentrations are generally reached between 1 and 4 h [24–27] or 3–7 h [28,29] after oral intake. The syrup has a faster absorption rate than the capsules but the two formulations are bioequivalent in extent of absorption [5,23,29].

Distribution

Ethosuximide distributes homogeneously throughout the body. Ethosuximide concentrations in saliva, tears and cerebrospinal fluid (CSF) are similar to plasma ethosuximide concentrations [30–34]. In three studies (involving 6, 15 and 19 patients) the correlation coefficients for the relationships between saliva and serum concentrations were 0.99, 0.99 and 0.74, respectively [32–34]. A fourth study, which examined ethosuximide concentrations in paired parotid saliva and plasma samples in 10 patients, showed that the average saliva to plasma ratio was 1.04 and appeared to be constant over the measured time intervals [32]. Based on these results, it has been concluded that saliva can be used in lieu of plasma for the therapeutic monitoring of ethosuximide.

In humans, ethosuximide's apparent volume of distribution is about 0.6–0.7 L/kg in adults and in children, implying distribution through total body water [23,24,26]. The binding of ethosuximide to plasma proteins is <10% [5].

Ethosuximide crosses the placenta in humans and has been detected in cord serum and amniotic fluid at concentrations similar to maternal serum concentrations [5,35]. Ethosuximide was detected in the urine or plasma of a newborn infant of a woman receiving chronic ethosuximide therapy in two separate reports [36,37]. The newborn infant's serum ethosuximide concentration was similar to that observed in the mother [37].

Ethosuximide is also excreted in the breast milk of mothers on chronic ethosuximide therapy. In multiple studies the average breast milk to maternal serum concentration ratio ranged from 0.8 to 0.94 [37–40]. The serum ethosuximide concentrations in breastfeeding infants of mothers on chronic ethosuximide therapy were 30–50% of their mother's serum ethosuximide concentrations [39,40].

Elimination

Metabolism is the main route of ethosuximide elimination in humans and animals. The drug undergoes extensive oxidative biotransformation (about 80%) to pharmacologically inactive metabolites, with only minor amounts (10–20%) being excreted unchanged in the urine, bile and faeces [5,41]. *In vitro* studies suggest that in humans the oxidation of ethosuximide is catalysed mainly by the cytochrome P450 (CYP) enzyme CYP3A4, with a minor contribution of CYP2E1 [42].

The major metabolite recovered in the urine of patients receiving ethosuximide is 2-(1-hydroxyethyl)-2-methylsuccinimide, of which at least 40% is excreted as a glucuronide conjugate [4]. Two other ethosuximide metabolites recovered (often as a glucuronide conjugate) from the urine of patients receiving ethosuximide are 2-ethyl-3-hydroxy-2-methylsuccinimide and 2-(2-hydroxyethyl)-2-methylsuccinimide. This latter metabolite can undergo subsequent metabolism by the hepatic mixed-function oxidase system to form the fourth major metabolite, 2-carboxymethyl-2-methylsuccinimide [4] (Fig. 39.1). Many of these metabolites occur as different stereoisomers. A recent study using a chiral assay identified 2-ethyl-2-hydroxymethylsuccinimide as an additional metabolite [43].

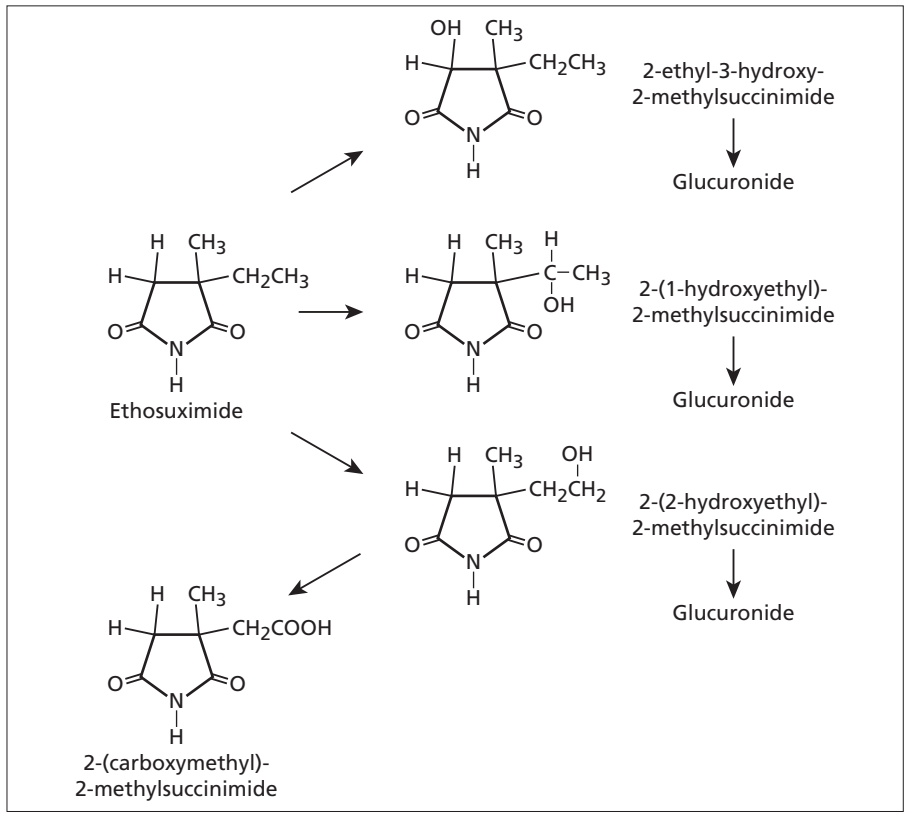

Fig. 39.1 Structure and biotransformation pathways of ethosuximide. Reproduced with permission from ref. 4.

In humans, ethosuximide's elimination follows first-order kinetics. Its apparent oral clearance in adults averages about 10 mL/kg/h [25,26] and in two children it was 13 mL/kg/h and 16 mL/kg/h [23]. This is much lower than the rate of hepatic plasma flow (0.9 L/kg/h), implying that ethosuximide does not undergo a significant first-pass effect and that its clearance is not blood flow limited. The clearance of ethosuximide has been reported to decrease slightly after repeated dosing. Ethosuximide does not induce the hepatic microsomal CYP enzymes or the uridine diphosphate glucuronosyltransferase (UDPGT) system [44–46]. Autoinduction does not occur, unlike in rats [46,47].

Ethosuximide has a relatively long half-life that varies with age. Ethosuximide's mean half-life in adults not receiving enzyme inducers was reported to range from 40 to 70 h compared with 30–40 h in children [23–29,47,48]. There are large variations reported in ethosuximide's half-life (15–68 h) in the paediatric studies [23,24,49]. The half-life of ethosuximide has been reported to be 32–41 h in neonates [37,39]. The time to reach steady-state concentrations following a dosage change is 6–7 days for children and 12 days for adults. Clearance is reported to be lower in women than in men [50]. Dose size and repeated dosing do not affect ethosuximide half-life [24,49].

Pharmacokinetics in special populations

As discussed in the section above, children have higher ethosuximide clearance values and shorter half-lives than adults [23–29,47,48].

There is very limited information on potential changes in ethosuximide pharmacokinetics during pregnancy. Available evidence suggests that ethosuximide clearances increases during prenancy compared withy the pre-pregnant state [51].

The effects of liver and renal disease on ethosuximide elimination have not been formally studied. Theoretically, liver disease would be expected to impair ethosuximide elimination due to ethosuximide's substantial hepatic oxidative metabolism, while the effect of renal disease on ethosuximide elimination should have much less impact. Haemodialysis can readily remove ethosuximide. One report estimated that approximately 50% of the body's ethosuximide was removed over a 6-h dialysis interval and that ethosuximide half-life dropped to 3–4 h during dialysis [52]. In a separate case report, peritoneal dialysis was able to decrease ethosuximide concentrations in a child taking both ethosuximide and phenobarbital [53].

Drug interactions

Effects of other drugs on ethosuximide pharmacokinetics

Concomitant therapy with enzyme-inducing antiepileptic drugs (AEDs) such as carbamazepine, phenytoin and barbiturates increases the rate of ethosuximide metabolism. As a result, ethosuximide's clearance is significantly accelerated (leading to a drop in the serum concentration) when ethosuximide is used concurrently with phenobarbital, primidone, phenytoin or carbamazepine [26,54–56]. In a formal comparative study in adults, ethosuximide's apparent oral clearance was found to be, on average, 15.3 mL/kg/h in patients taking enzyme-inducing AEDs, compared with 9.2 mL/h/kg in controls not taking enzyme inducers [26]. The half-life was also shorter in patients on enzyme inducers than in controls (54 h versus 29 h respectively). Discontinuation of concomitant carbamazepine therapy in one study resulted in a 48% increase in plasma ethosuximide concentrations [57]. The magnitude of the effect of enzyme-inducing AEDs on ethosuximide pharmacokinetics varies considerably between patients [54].

The effect of valproic acid on the pharmacokinetics of ethosuximide is variable, with different studies showing ethosuximide's clearance increased, decreased or unchanged when concomitant valproic acid therapy was employed [44,47,48,55,58–61].

There have not been any formal pharmacokinetic interaction studies examining potential ethosuximide interactions with felbamate, gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, pregabalin, vigabatrin or zonisamide.

Interactions with non-antiepileptic medications have been occasionally reported. The clearance of ethosuximide is substantially increased by co-medication with rifampicin, a CYP3A4 inducer [56]. In one report, use of ethosuximide and isoniazid, a potent inhibitor of CYP enzymes, resulted in increased serum ethosuximide concentrations and psychotic behaviour [62].

Effect of ethosuximide on the pharmacokinetics of other drugs

Ethosuximide has a low potential for drug interactions due to its lack of effect on most drug-metabolizing enzymes. Most authors conclude that ethosuximide therapy does not have a clinically significant effect on the pharmacokinetics of phenytoin, phenobarbital or carbamazepine, although there are scattered reports of some changes in serum phenytoin or phenobarbital concentrations when ethosuximide is used in combination with phenytoin or primidone [58,63–69]. There is neither an alteration in the plasma protein binding of carbamazepine or phenytoin nor a change in the formation of phenobarbital from primidone when ethosuximide is used [70].

One study reported a decrease in serum valproic acid concentration following the addition of ethosuximide [from 120.0 ± 20.1 μg/mL pre-ethosuximide to 87.0 ± 13.1 μg/mL during co-therapy with ethosuximide ($P < 0.01$)] [71]. Following cessation of ethosuximide, valproic acid levels rose by 36.7%. The mechanism underlying this effect is unknown.

Ethosuximide has not been found to interact with oral contraceptive hormones [5].

Pharmacodynamic drug interactions

Despite equivocal evidence from animal studies [72,73], clinical observations suggest that valproic acid and ethosuximide may display a favourable pharmacodynamic interaction, in that patients refractory to either drug given alone may respond well to the combination [74–76].

Serum level monitoring

Although ethosuximide treatment is usually individualized by direct observation of clinical response supplemented by electro-

encephalogram (EEG) recordings, measurements of serum ethosuximide concentrations may be valuable as an aid to dosage adjustments in patients with difficult-to-control seizures or suspected drug toxicity, in patients susceptible to pharmacokinetic alterations (e.g. during pregnancy, in disease states, or when adding or withdrawing potentially interacting drugs) or as a check for compliance. The majority of patients are expected to respond at serum ethosuximide concentrations between 40 and 100 μg/mL, but in some cases serum levels below or above this range may be required [77].

Efficacy

Although there are no high-quality double-blind controlled monotherapy trials rigorously proving ethosuximide's efficacy against typical absence seizures [78,79], a powerful anti-absence effect of ethosuximide was suggested by two open studies conducted in the 1970s by Browne *et al*. [80] and Sherwin *et al*. [81], and since then there has been general consensus that ethosuximide is an effective first-line monotherapy for typical absence seizures.

In the trial by Browne *et al*. [80], ethosuximide's efficacy was examined with a well-constructed methodology for patient selection and assessment. In order to enrol, each patient's absence seizures were required (a) to meet a predetermined clinical definition of an absence seizure; and (b) be witnessed by the principal investigator. Seizure frequency was then assessed by five separate measures, including (a) ward staff observation; (b) trained observer observation; (c) parent's observation; (d) physician observation (including during patient hyperventilation); and (e) standardized video-electroencephalographic recording. These five measures were combined into a 'seizure index'. Thirty-seven patients enrolled. By the eighth week of treatment, 19% (7/37) were seizure free with a 100% reduction in seizure index. Overall, during ethosuximide therapy, 49% (18/37) demonstrated ≥90% reduction in seizures while 95% (35/37) exhibited a ≥50% reduction in seizures. The anti-absence effect was noted rapidly (within a week) for any given ethosuximide dose. Plasma ethosuximide concentrations ranged from 16.6 to 104.0 μg/mL (doses 6.5–36.7 mg/kg) and, based on the seizure index, the authors suggested an optimal range of plasma ethosuximide concentrations of 40–100 μg/mL.

The second major open-label non-comparative trial, conducted by Sherwin *et al*. [81], also had a prospective longitudinal design and used therapeutic drug monitoring to maximize clinical response. Seventy patients enrolled. The group was 54% (38/70) female with ages ranging from 4 to 28 years (median 12 years). Thirty-eight patients (54%) had only absence seizures, while the remaining had either absence seizures with tonic–clonic seizures (30%) or absence seizures and one or more other generalized seizure types (16%). Approximately half the patients were on other AEDs in addition to ethosuximide. Patients received between 9.4 and 73.5 mg/kg/day and were evaluated at 6-month intervals. Introduction of ethosuximide therapy resulted in complete control of absence seizures in 47% (33/70) of the patients. None of these patients had plasma ethosuximide concentrations below 30 μg/mL, and only 9% had levels below 40 μg/mL. During the next 2.5 years, attempts were made to achieve plasma ethosuximide concentrations above 40 μg/mL in the remaining patients (53%, 37/70) with uncontrolled absence seizures. Improved compliance and higher ethosuximide dosages led to significantly higher ethosuximide plasma concentrations in 19 patients; 10 of these 19 patients became free from absence seizures. At the 2.5 years follow-up mark, 61% (43/70) of the group was free from absence seizures. In these patients, ethosuximide's effectiveness persisted over the next 2.5 years (total 5 years) of follow-up. Ethosuximide, however, was not able to control absence seizures in patients with absence seizures and tonic–clonic seizures on combination AED therapy.

A number of controlled comparative trials have provided evidence that ethosuximide and valproic acid have similar efficacy against absence seizures [82–86]. These studies utilized clinical observation only ($n = 2$), video-electroencephalographic telemetry only ($n = 1$) or both techniques ($n = 2$) to assess response to therapy. Success was defined as 100% seizure control. In these comparative trials, ethosuximide therapy resulted in 100% seizure reduction in 58% of patients utilizing clinical observation and 57% of patients using video-electroencephalographic telemetry. Serum ethosuximide concentrations ranged from 26 to 114 μg/mL. In comparison, valproic acid therapy resulted in 100% seizure reduction in 63% of patients (using clinical observation) or 55% of patients (using video-electroencephalographic telemetry), with serum valproic acid concentrations ranging from 32 to 131 μg/mL.

One open-label study found the combination of ethosuximide and valproic acid effective in five patients with absence seizures refractory to either drug given in monotherapy [74]. Subsequently, many authors have recommended ethosuximide and valproic acid combination therapy for patients with absence seizures resistant to monotherapy [29,87]. Similarly, in patients with both absence and tonic–clonic seizures, ethosuximide has been used in combination with another AED effective against tonic–clonic seizures, such as valproic acid, carbamazepine or phenytoin. Despite being reported as 'highly effective' against atypical absence seizures [87], patients with atypical absence seizures are generally more resistant to drug treatment and ethosuximide is almost always used as part of combination therapy in these patients due to the high incidence of co-existing seizure types.

There is some evidence that ethosuximide is useful in the prevention and treatment of absence status epilepticus at serum concentrations greater than 120 μg/mL [88,89]. There are also reports of ethosuximide being effective in patients with severe myoclonic epilepsy in infancy [90], childhood epileptic encephalopathy (Lennox–Gastaut syndrome) [91], juvenile myoclonic epilepsy [92,93], epilepsy with myoclonic absences [93,94], eyelid myoclonia with absences [76,93], early-onset absence epilepsy and paroxismal dyskinesia [95], epilepsy with continuous spikes and waves during slow-wave sleep [75] and Landau–Kleffner syndrome [96], Angelman's syndrome [97], photosensitive seizures [98] and gelastic seizures [29,99]. Evidence of effectiveness in these conditions typically comes from uncontrolled studies and small case series, and in many difficult-to-control patients ethosuximide is often combined with other AEDs, particularly valproic acid. There are also no controlled studies investigating ethosuximide's effectiveness against simple partial, complex

partial or secondary generalized tonic–clonic seizures. However, recent reports suggest that ethosuximide can be effective in the treatment of epileptic negative myoclonus associated with childhood partial epilepsy [100,101].

Adverse effects

Ethosuximide's adverse effects can be divided into four categories: (a) commonly observed; (b) infrequent, but clinically relevant; (c) rare, potentially life-threatening; and (d) manifestations of overdose. Like most drugs, the most commonly observed adverse effects are directly related to the primary and secondary pharmacological effects of the drug and are usually predictable, dose dependent, host independent and resolve with dose reduction. The infrequent but clinically relevant adverse effects may result from multiple mechanisms including (a) dose-dependent and readily reversible effects related to the drug's main pharmacological actions; (b) idiosyncratic reactions; (c) effects of long-term therapy related to the cumulative dose; and (d) other delayed effects, such as teratogenicity. Most idiosyncratic drug reactions cannot be predicted based upon the known pharmacological effect of the drug, do not demonstrate a simple dose–response relationship, are host dependent, and some can be serious and life threatening [102].

Common adverse effects

Twelve large clinical trials (each involving over 50 patients) published between 1958 and 1966 detailed the spectrum of ethosuximide's adverse effects [103–114]. Browne [115] summarized these studies and found that the overall incidence of ethosuximide-related adverse effects ranged from 26% to 46% (Table 39.1). In half of these large trials, 37% or more of the subjects experienced ethosuximide-related adverse effects [115].

Gastrointestinal effects

The most common concentration-dependent adverse effects involve the gastrointestinal system. These include nausea (the most common), abdominal discomfort, anorexia, vomiting and diarrhoea [3,29,115,116]. Symptoms usually occur at the onset of therapy, are mild in severity, affect 20–33% of children and resolve promptly after dose reduction [29,115]. In some patients, gastrointestinal effects are transient and no dose reduction is needed; in others, dividing the total daily dosage and administering the smaller doses at meal time helps lessen the symptoms [115]. Infrequently, gastrointestinal symptoms are severe enough to cause discontinuation of the drug.

Table 39.1 Summary of adverse effect profiles noted in early studies involving 50 or more subjects receiving ethosuximide (12 reports, 1958–1966).

Adverse effect	Range of reported frequencies (median) (%)
Any adverse effect	26–46 (37)
Gastrointestinal distrurbances (nausea, abdominal discomfort, anorexia, vomiting and diarrhoea)	4–29 (13)
Drowsiness	0–16 (7)
Rash	0–6 (0)
Ataxia	0–1 (0)
Dizziness	0–4 (1)
Hiccoughs	0–5 (0)
Irritability	0 (0)

Modified from ref. 115 with permission.

Neurological effects

The second most common form of concentration-dependent adverse effects relate to the central nervous system (CNS) [115]. Similar to the gastrointestinal effects, drowsiness usually occurs at the onset of therapy and resolves promptly when the ethosuximide dose is reduced [115].

Additional CNS effects include insomnia, nervousness (12% of children), dizziness, hiccoughs, lethargy, fatigue, ataxia and behaviour changes (e.g. aggression, euphoria, irritability, hyperactivity) [5,79,116]. A direct relationship between behavioural changes and ethosuximide therapy is not certain since poor study methodology makes analysis of existing reports difficult at best. The lack of reliable methods for objectively measuring behaviour changes, the confounding variables of polypharmacy and the lack of serum AED concentrations during the studies are examples of these methodological concerns.

Headaches occur in approximately 14% of children taking ethosuximide. In contrast to the other neurological side-effects described above, headaches do not appear to be concentration dependent, may not respond to dose reduction and may be persistent [116,117].

Assessing ethosuximide's effects on cognition is difficult. Few clinical trials have examined the issue in a controlled fashion, accounting for confounding variables such as serum drug concentrations, underlying mental retardation, concomitant AEDs or seizure type. Memory, speech and emotional disturbances were noted on psychometric testing in 25 children receiving ethosuximide for various seizure types in one early report [118]. However, all the patients were also on barbiturates, 60% of the cohort had intelligence quotient (IQ) scores below 83, serum ethosuximide concentrations were not measured and no matched control group was used. In contrast, ethosuximide therapy resulted in significant improvement in verbal and full-scale IQ scores without change in motor performance or personality test scores in a cohort of children without epilepsy but with learning disorders and 14 and 6 per second positive spikes on EEG [119]. Similarly, psychometric performance improved significantly over 8 weeks of ethosuximide therapy in 17 of 37 (46%) children with absence seizures in a well-designed study [80]. This improvement was significantly different compared with a control group of patients tested in the same fashion over the same interval. Only 25% of the study group had IQ scores less than 83 and only 32% were on other AEDs [80].

Infrequent, but clinically relevant adverse effects

Psychiatric effects

Some patients taking ethosuximide have developed episodes of psychotic behaviour manifested by anxiety, depression, visual

hallucinations, auditory hallucinations and intermittent impairment of consciousness [105,120–122]. The patient's age (young adults in their teens or twenties) and a history of mental illness are risk factors for these adverse effects [115]. The acute psychotic episodes appeared following ethosuximide-induced seizure control with associated EEG improvement. The episodes resolved when ethosuximide was stopped and seizures returned, possibly illustrating the phenomenon of 'forced normalization'. Psychotic symptoms have recurred when ethosuximide was re-started in patients with previous ethosuximide-related psychotic episodes. Among all anti-absence AEDs, this 'forced normalization' reaction occurs with highest frequency with ethosuximide and is not dose dependent [6,123]. This type of adverse effect seldom occurs in young children with no previous history of psychiatric disease receiving ethosuximide for typical absence seizures [115].

Neurological effects

No evidence of ethosuximide-associated seizure exacerbation is found in most studies [80,107,112,114]. Exacerbation of myoclonic and absence seizures and transformation of absence into 'grand mal' seizures in patients receiving ethosuximide are reported in scattered publications [124,125]. This 'exacerbation' effect is likely to be simply a consequence of the relatively high incidence of generalized tonic–clonic seizures in patients with absence seizures, coupled with ethosuximide's lack of efficacy against generalized tonic–clonic seizures. A recent report also failed to identify any evidence for a precipitating effect of ethosuximide on generalized tonic–clonic seizures [126].

Long-term cumulative-dose adverse effects of ethosuximide are infrequent. Extrapyramidal reactions (e.g. severe bradykinesia, akasthesias, akathisia, dyskinesias and parkinsonian syndrome) have been noted after several years of ethosuximide treatment [106,127].

Haematological effects

The incidence of ethosuximide-related granulocytopenia ranged from 0% to 7% in early studies [115]. This symptom has been considered probably dose dependent since it often resolved with dose reduction without requiring termination of ethosuximide therapy. It is critical to distinguish between this probably dose-dependent haematological adverse effect and ethosuximide-associated idiosyncratic bone marrow depression (see below). Careful clinical and laboratory monitoring is essential in making this distinction.

Other organ systems

Ethosuximide therapy is not reported to cause serious endocrine adverse effects [115]. Ethosuximide can precipitate an attack of acute intermittent porphyria [117,128].

Little information is available about the overall risks that maternal ethosuximide use poses to the fetus. There are currently not enough data to assess accurately the teratogenic effect of ethosuximide in humans. One study found that 2 out of 13 newborns born to 10 women with epilepsy taking ethosuximide had major malformations (bilateral clefting, hare-lip) [39]. In addition, the cohort had a higher rate of minor abnormalities compared with a pair-matched control group of newborns of women without epilepsy. The mothers of these two seriously affected newborns were on ethosuximide in combination with phenobarbital in one case and primidone in the other. In another small series, one of five infants born to a mother taking ethosuximide was malformed [129].

Rare, potentially life-threatening adverse effects

Ethosuximide has been associated with a wide variety of idiosyncratic reactions [5,102,116] including allergic dermatitis, rash, erythema multiforme, Stevens–Johnson syndrome, systemic lupus erythematosus, a lupus-like syndrome, blood dyscrasias (aplastic anaemia, agranulocytosis), liver toxicity, autoimmune thyroiditis and diminished renal allograft survival.

The most common idiosyncratic reactions involve the skin. Allergic dermatitis and rash frequently resolve following ethosuximide withdrawal, but some patients may require steroid therapy. Patients developing Stevens–Johnson syndrome require hospitalization for more aggressive therapy.

Ethosuximide-associated blood dyscrasias can involve any or all cell lines ranging from thrombocytopenia to pancytopenia and aplastic anaemia. Only eight cases of ethosuximide-associated aplastic anaemia were reported between 1958 and 1994, with onset 6 weeks to 8 months after ethosuximide initiation [130]. Six patients were on polypharmacy, five taking either phenytoin or ethotoin in combination with ethosuximide. Despite therapy, five of the eight patients died.

Manifestations of overdose

The manifestations of acute ethosuximide overdose include nausea, vomiting and symptoms of CNS depression including stupor and coma leading to respiratory depression. The management of ethosuximide overdose involves life support measures, symptomatic treatment, procedures to decrease drug absorption and procedures to enhance drug elimination. Life support measures involve initial and immediate evaluation and stabilization of the patient's airway, breathing and circulation. Symptomatic treatment focuses on the subsequent care for each of the patient's overdose symptoms as they occur. No specific antidote exists for an ethosuximide overdose.

Methods to decrease absorption

Since ethosuximide overdose can rapidly lead to significant alteration of consciousness, induction of emesis is not recommended [131]. Administration of activated charcoal as an aqueous slurry may reduce absorption in conscious patients able to protect their airway. The effectiveness of activated charcoal is greatest if given within 1 h of an ethosuximide overdose [131]. The recommended dose of activated charcoal is 1 g/kg of weight for infants up to 1 year old, 25–50 g in children between 1 and 12 years old and 25–100 g in adults. The optimal dose has not been established [132]. If emesis or rapid deterioration of consciousness occurs or is impending, only personnel skilled in airway management should administer activated charcoal to minimize the potential for aspiration. The contraindications for the use of activated charcoal are a patient with an unprotected airway or if the therapy increases the risk or severity of aspiration [132].

Gastric lavage with a large-bore orogastric tube may be considered if a potentially life-threatening amount of ethosuximide has been ingested and the procedure can be performed within 1 h

of the ingestion [133]. Gastric lavage should not be employed routinely in the management of patients following an overdose of ethosuximide due to the risk of significant morbidity associated with the procedure.

Methods to enhance drug elimination

Haemodialysis may be useful in the treatment of an ethosuximide overdose. This is based on an observed extraction efficiency of 61–100% in one study of four patients with chronic renal disease (supported by haemodialysis) who received a single dose of 500 mg of ethosuximide 4 h prior to dialysis. In this study, the elimination half-life of ethosuximide was reduced by dialysis to an average of 3.5 h [52]. There have been no reports of haemoperfusion use in ethosuximide overdose. Both exchange transfusion and forced diuresis have little place in the treatment of ethosuximide overdose since ethosuximide has low protein binding and little of the parent ethosuximide compound is excreted unchanged in the urine.

Place in current therapy

Indications

Ethosuximide and valproic acid are considered as treatment of choice for first-line monotherapy against typical absence seizures in an expert consensus guideline [134]. Paediatric consensus guidelines generally regard ethosuximide and valproic acid as treatment of choice for childhood absence epilepsy, whereas in juvenile absence epilepsy valproic acid is generally preferred because when adolescence is approached the risk of generalized tonic–clonic seizures increases [135,136].

Ethosuximide adjunctive therapy may be beneficial for (a) patients with typical or atypical absence seizures not controlled on ethosuximide or valproic acid monotherapy or (b) patients with both absence and tonic–clonic seizures, when absence seizures are not controlled by the concomitant drug [29,87,137]. There is no evidence supporting a role for ethosuximide monotherapy or ethosuximide adjunctive therapy in patients with only primary generalized tonic–clonic seizures or in patients with only simple partial, complex partial or secondary generalized tonic–clonic seizures.

Additional conditions where ethosuximide may be useful include absence status epilepticus [88,89], severe myoclonic epilepsy in infancy [90], childhood epileptic encephalopathy (the Lennox–Gastaut syndrome) [91], juvenile myoclonic epilepsy [92,93], epilepsy with myoclonic absences [93,94], eyelid myoclonia with absences [76,93], early-onset absence epilepsy and paroxismal dyskinesia [95], epilepsy with continuous spikes and waves during slow-wave sleep [75] and Landau–Kleffner syndrome [96], Angelman's syndrome [97], photosensitive seizures [98], gelastic seizures [29,99] and epileptic negative myoclonus associated with childhood partial epilepsy [100,101]. In some of these syndromes, ethosuximide is usually combined with other drugs possessing a broader spectrum of antiseizure activity.

Dose and titration rates

A common starting dose for children is 10–15 mg/kg/day. Subsequent titration is performed according to the patient's clinical response. In older children and adults ethosuximide is often initiated at 250 mg/day and increased by 250-mg increments until the desired clinical response is reached. Ethosuximide can be administered either as once-, twice- or even thrice-daily dosing (with meals) to maximize seizure control while minimizing adverse effects. The interval between dosage changes for older children and adults varies from 3 days to every 12–15 days.

In younger children, maintenance dosages frequently range from 15 to 40 mg/kg/day [87]. For older children and adults, common maintenance doses are 750–1500 mg/day. When used in elderly patients, ethosuximide should be titrated using smaller increments with longer intervals between changes. The time to reach steady-state concentration following a dosage change is 6–7 days for children and 12 days for adults.

If the clinical situation warrants discontinuing ethosuximide (e.g. intolerable side-effects without seizure control or ≥2 years free of absence seizures), then gradual reduction over 4–8 weeks is recommended. If necessary, abrupt discontinuation is probably safe due to ethosuximide's long half-life.

Laboratory monitoring

There is no evidence that monitoring of blood counts during ethosuximide therapy allows early prediction of ethosuximide's idiosyncratic haematological reactions. Patient education is important. Patients need to watch for fever, sore throat and cutaneous or other haemorrhages, and alert their physician immediately if these symptoms occur. However, one recommendation for blood monitoring has been that 'periodic blood counts be performed at no greater than monthly intervals for the duration of treatment with ethosuximide and that the dosage be reduced or the drug discontinued should the total white-blood-cell count fall below 3,500 or the proportion of granulocytes below 25% of the total white-blood-cell count' [138].

Ethosuximide should always be titrated to clinical response (i.e. maximal seizure control with minimal adverse effects). The generally accepted reference range for serum ethosuximide concentration is 40–100 μg/mL, but some patients with refractory seizures or absence status may need serum concentrations up to 150 μg/mL. In selected cases, monitoring of serum ethosuximide concentration may aid in maximizing seizure control and in identifyng non-compliance [81].

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40 Felbamate

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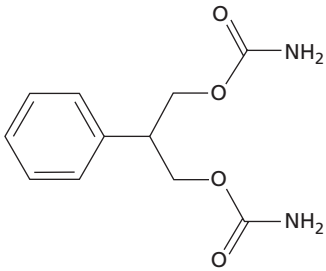

Primary indications	Add-on treatment of Lennox–Gastaut syndrome and partial and secondary generalized seizures in patients refractory to other agents
Usual preparations	Tablets: 400, 600 mg; syrup: 600 mg/5 mL
Usual dosages	Initial: 1200 mg/day (adults); 15 mg/kg/day (children). Maintenance: 1200–3600 mg/day (adults); 15–80 mg/kg/day (children)
Dosing frequency	2–4 times/day
Significant drug interactions	Felbamate increases the serum levels of phenobarbital, phenytoin, valproic acid, *N*-desmethylclobazam and carbamazepine-10,11-epoxide. Felbamate lowers serum levels of carbamazepine and contraceptive sterioids. Phenytoin, carbamazepine and, possibly, phenobarbital lower serum felbamate levels. Valproic acid increases serum felbamate levels
Serum level monitoring	May be useful in selected cases
Reference range	30–60 mg/L
Common/important adverse effects	Liver toxicity and aplastic anaemia are rare but serious. Additionally, insomnia, headache, anorexia, weight loss, fatigue, dizziness, lethargy, mood and behavioural changes, ataxia, visual disturbances, gastrointestinal symptoms or rash
Main advantages	Highly efficacious in some patients with Lennox–Gastaut syndrome
Main disadvantages	Liver toxicity and aplastic anaemia. Other adverse effects are frequent on initial therapy, and with polytherapy
Mechanisms of action	Blockade of sodium channels, potentiation of $GABA_A$-mediated inihibition and antagonism of NMDA-mediated responses
Oral bioavailability	90%
Time to peak levels	1–6 h
Elimination	Hydroxylation and then conjugation (60%) and renal excretion in unchanged form (40%)
Volume of distribution	0.8 L/kg
Elimination half-life	11–25 h (lowest in patients co-medicated with enzyme inducers)
Plasma clearance	20–40 mL/kg/h in adults (highest in patients co-medicated with enzyme inducers). Higher values are reported in children
Protein binding	20–25%
Active metabolites	None
Comment	Highly effective in severe refractory cases, but use limited by hepatic and haematological toxicity

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Introduction

Felbamate (Felbatol®, Taloxa®) was synthesized by Wallace Laboratories in the USA in 1954 [1]. The Antiepileptic Drug Development (ADD) programme of the National Institutes of Health (NIH) identified its potential for anticonvulsant activity in the 1980s [2,3]. Extensive clinical trials ensued, resulting in Food and Drug Administration (FDA) approval on 30 July 1993 for use in the USA as adjunctive and monotherapy in adults with partial seizures with or without secondary generalization, and as adjunctive therapy in children with Lennox–Gastaut syndrome. The unexpected development of aplastic anaemia prompted the FDA and manufacturer Carter Wallace to issue a strong warning regarding continued use of felbamate on 1 August 1994. Reports of felbamate-associated hepatic failure also engendered further concern. As a result, felbamate is not indicated as a first-line treatment and its use should be reserved for a few patients who respond inadequately to alternative antiepileptic drugs (AEDs) and whose epilepsy is severe enough that the risk of aplastic anaemia and/or liver failure is deemed acceptable by the patient compared with the benefits conferred by its use. Because of the effectiveness of this drug in many patients, felbamate remains on the market in the USA and is available for limited use in other countries.

Chemistry

Felbamate (2-phenyl-1,3-propanediol dicarbamate) has a chemical formula corresponding to $C_{11}H_{14}N_{12}O_{14}$ and a molecular weight of 238.43. It is chemically related to the anti-anxiety drug meprobamate. Felbamate is a white crystalline powder, with a melting point of 151–152°C, and is relatively insoluble in water and ethanol.

A number of methods have been developed to measure felbamate and its metabolites in biological samples. A high-performance liquid chromatography method for the simultaneous analysis of felbamate, phenytoin, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, carbamazepine, carbamazepine-10,11-epoxide and carbamazepine 10,11-diol in serum that could separate the compounds of interest and three internal standards in less than 15 min has been developed using a mobile phase optimization technique [4]. Some methods can measure felbamate concentrations in as little as 0.1 mL of plasma [5]. Other methods can measure felbamate and its three metabolites in brain and heart tissue homogenates [6].

Pharmacology

Activity in experimental models of seizures and epilepsy

Animal model testing demonstrated a broad spectrum of activity against different seizure types. Felbamate inhibits seizures induced by maximal electroshock, pentylenetetrazol and picrotoxin, but seizures induced by bicuculline and strychnine are not affected [2]. The drug is protective against epileptiform activity induced by the potassium channel blocker 4-aminopyridine [7]. Thus, felbamate seems to both increase seizure threshold and prevent seizure spread [2]. This profile in animal models would predict action against both partial and generalized (including absence) epilepsies in humans. Felbamate has also been found to be active in two rat models of status epilepticus [8,9], and to be effective in preventing the expression of stage 5 kindled seizures in corneal-kindled rats [3].

Table 40.1 Protective index (median toxic dose/median effective dose) of felbamate and standard antiepileptic drugs in various animal models of seizures.

Drug	Maximal electroshock	Pentylenetetrazole	Picrotoxin	NMDA	Kindling
Felbamate	16.3	5.51	5.2	146	35.8
Carbamazepine	8.1	NP	37.2	16	>17.3
Ethosuximide	NP	3.4	1.8	4	NP
Phenytoin	6.9	NP	NP	71	NP
Valproic acid	1.6	2.9	1.1	5.8	7.3

Adapted from refs 2, 3 and 36.
NP, not protective.

The anticonvulsant effects of felbamate against seizures induced by maximal electroshock are enhanced by combination with non-protective doses of phenytoin, carbamazepine, valproic acid or phenobarbital in mice. This effect could not be accounted for by a pharmacokinetic mechanism and thus implies a pharmacodynamic interaction [10]. Also, a single subprotective dose of felbamate combined with diazepam enhanced the effects of diazepam against seizures induced by maximal electroshock, pentylenetetrazol and isoniazid [11]. In addition to its anticonvulsant action, felbamate has a neuroprotective effect in various animal models [9,12,13]. Felbamate has a very favourable protective index in animals compared with other AEDs (Table 40.1).

Mechanisms of action

Although the specific mechanism by which felbamate exerts its anticonvulsant effects is unknown, evidence exists for a number of possible mechanisms. The *N*-methyl-D-aspartate (NMDA) receptor is the site of action where felbamate was found to be effective against NMDA-induced clonus in mice [3]. Inhibition of [^{3}H]-5,7-dichlorokynurenic acid (a high-affinity glycine receptor antagonist) binding corresponding with peak plasma and brain concentrations of felbamate has been demonstrated [14]. Felbamate may have dual actions in the brain, both inhibiting NMDA responses and potentiating the effects of γ-aminobutyric acid (GABA) by an action at a site on the $GABA_A$ receptor which is distinct from the binding sites of GABA and benzodiazepine drugs [2,15,16]. Felbamate has also been found to be effective in blocking sustained repetitive firing in mouse spinal cord neurones, suggesting inhibition of sodium channel conductance [3].

Pharmacokinetics

Absorption

Felbamate is rapidly and completely absorbed after oral administration, with peak serum concentrations occurring 1–6 h after

intake [17–19]. The bioavailability is similar for the tablets and the suspension, and is not affected by food [20,21].

Distribution

Animal studies have shown that felbamate distributes rapidly into a number of tissues, including brain [22], and crosses the placenta [23]. Felbamate extraction into brain in a single transcapillary passage was found to be 5–20%, and the drug was found to distribute relatively uniformly throughout the brain [24]. The apparent volume of distribution is estimated at about 0.8 L/kg.

In humans, 20–25% of the total plasma concentration is bound to plasma proteins, primarily to serum albumin.

Elimination

The half-life of felbamate in healthy volunteers is approximately 20 h and ranges from 13 to 23 h when given as monotherapy to adult patients with epilepsy [17,20]. Multiple dosing does not appear to alter the elimination half-life. In patients with epilepsy receiving either phenytoin or carbamazepine, however, the half-life of felbamate was shorter, approximately 13–14 h with a range of 11.4–19.6 h [19]. Thus, phenytoin and carbamazepine increase the rate of felbamate elimination, whereas valproic acid has the opposite effect [20,25].

Felbamate is partly eliminated unchanged in urine and is partly metabolized in the liver via hydroxylation followed by conjugation. A number of potentially toxic metabolites may be formed [26–28]. This hepatic metabolism sets the stage for drug interactions with concomitantly administered medications metabolized via similar pathways.

In human volunteers, 40–49% of a felbamate dose is recovered in the urine as the parent compound, with the rest as various metabolites [17]. Metabolites do not contribute significantly to activity in animal models of epilepsy [2]. However, in humans, felbamate may be metabolized to lead to the formation of 2-phenylpropenal, an α,β-unsaturated aldehyde (atropaldehyde) which is a potent electrophile [29]. Atropaldehyde has been proposed to play a role in the development of liver and bone marrow toxicity during felbamate therapy. It undergoes rapid conjugation with glutathione in most individuals. This has led to analysing urine samples from patients receiving felbamate for two atropaldehyde-derived mercapturic acids, as a possible method for monitoring patients [30].

Pharmacokinetics in special populations

In agreement with results from animal studies [22,31], the apparent oral clearance of felbamate has been found to be 20–65% higher in children, particularly young children, than in adults [32–34]. Thus, children may need a higher dose per kilogram than adults. Drug interactions affecting felbamate clearance in children are similar to those in adults. In a study of children using the non-linear mixed effects model (NONMEM) programme for describing pharmacokinetics, the clearance of felbamate was found to be increased by 49% and 40%, respectively, when the drug was used in combination with carbamazepine and phenytoin. Conversely, valproic acid and older age were found to decrease felbamate clearance [32].

In a study that assessed felbamate pharmacokinetics in 24 elderly (66–78 years) and 11 young (18–45 years) subjects, felbamate clearance after a single dose was found to be about 20% lower in the elderly than in the young (31.2 versus 25.1 mL/min). Felbamate was also less well tolerated in elderly subjects than in young subjects, as shown by higher rates of adverse event reporting and dropouts when multiple doses were given. It was concluded that elderly subjects require lower initial dosing and slower dose titration of felbamate than non-elderly adults [35].

As would be expected from a drug 40–50% eliminated unchanged in the urine, persons with renal failure will need lower doses of felbamate, with urinary clearance representing only 9–22% of overall clearance in these patients [36]. In patients with creatinine clearance values between 5 and 10 mL/min, the apparent oral clearance of felbamate was one-half that found in healthy control subjects.

Drug interactions

As discussed above, the metabolism of felbamate is accelerated by concomitant treatment with phenytoin or carbamazepine, resulting in an increase in felbamate clearance by about 40–50% [19,37,38]. Conversely, valproic acid decreases felbamate clearance by up to about 20% [20,21,25].

Felbamate may both induce and inhibit cytochrome P450 (CYP) drug-metabolizing enzymes [39–42]. Induction of carbamazepine metabolism by felbamate is responsible for a modest reduction (about 20%) in serum carbamazepine levels in patients started on add-on therapy with felbamate. In one study, serum carbamazepine concentrations decreased from 7.5 μg/mL during placebo treatment to 6.1 μg/mL during felbamate treatment ($P < 0.05$) [43]. On the other hand, mean carbamazepine-10,11-epoxide concentrations increased from 1.8 μg/mL during placebo baseline periods to 2.4 μg/mL during felbamate treatment [43]. The effect was evident after the first week of treatment and reached a plateau in 2–4 weeks [44]. Enzyme induction is also probably responsible for a decrease in serum levels of steroid oral contraceptives in women co-medicated with felbamate [45]. However, the most common interactions described in humans with felbamate involve inhibition of the metabolism of co-administered drugs, with a consequent increase in their serum concentration. Felbamate significantly increases the concentrations of phenytoin, and phenytoin dose decreases of about 20% were needed in the first major study of felbamate as an add-on drug to maintain stable phenytoin concentrations [46–48]. Felbamate has been found to increase the serum concentrations of phenobarbital [49,50] and *N*-desmethylclobazam metabolically derived from clobazam [51]. Valproic acid levels are also increased by felbamate. In one study of 10 patients on valproic acid monotherapy, valproic acid levels increased by 18% in the presence of 1200 mg felbamate per day and by 31% with felbamate doses of 2400 mg/day [52].

Although few studies are available regarding interactions with drugs other than AEDs, it can be anticipated that the elimination of other substances cleared by CYP enzymes will be either induced or inhibited by felbamate.

Serum level monitoring

In the initial double-blind study in patients with partial-onset seizures, most serum levels of felbamate ranged between 20 and 45 μg/mL [46]. However, in post-marketing experience, concentrations between 40 and 100 mg/mL have been commonly found in persons responding favourably (Leppik, personal experience). In general, felbamate dosage can be individualized solely on the basis of clinical response. However, because there is a wide range of clearances for felbamate resulting from co-medication and other sources of individual variability, concentrations are not readily predictable from the doses, and measurement of blood levels can be useful to guide dosing.

A recent review has suggested a reference range for felbamate concentrations of 30–60 mg/L [53]. It was stressed, however, that variability in response at these concentrations is considerable and that higher concentrations may confer additional benefit, though they are also associated with a higher probability of adverse effects [53].

Efficacy

The first evidence that felbamate may be effective in humans came from a study of the pharmacokinetics of this drug [19]. Since then, a number of controlled trials have been performed, some of which used novel study designs, including use of presurgical patients, monotherapy studies with 'active placebos', and a study in patients with Lennox–Gastaut syndrome [54–56]. Many of these designs have been used subsequently in new AED development.

The first pivotal study was an NIH-sponsored, double-blind, placebo-controlled, two-centre add-on trial in patients with partial-onset seizures [46]. The mean seizure frequencies during the 8-week analysis periods in the 56 patients completing the study were 34.9 during the felbamate period and 40.2 during the placebo period ($P = 0.007$). Another NIH-sponsored study in patients with partial-onset seizures involved a triple cross-over of felbamate and placebo while carbamazepine was maintained as the stable AED. Initial analysis showed no significant difference in seizure frequency between placebo and felbamate periods, but when a correction was made for the lower carbamazepine level noted during felbamate periods, the data suggested a significant antiseizure effect of felbamate [57].

Two blinded studies using felbamate in patients with partial seizures undergoing presurgical evaluation have been performed [54,58]. In a multicentre study, 64 subjects were randomized to receive felbamate (30) or placebo (34) after the presurgical evaluation had been completed. Felbamate was titrated to 3600 mg over 3 days. The primary outcome variable was time to fourth seizure. Patients were hospitalized for 8 days for observation and, if they remained in the study, they were discharged and followed as outpatients for an additional 21 days. In the felbamate group, 54% made it to the end of the observation period without a fourth seizure, whereas only 12% of the placebo group made it to this endpoint (Kaplan–Meier analysis, $P = 0.002$) [54]. In the same study, during the presurgical evaluation phase as other AEDs were being lowered, the mean number of seizures was 2.05/day; during the felbamate treatment period, inpatient and outpatient, the seizure rate decreased to 0.29/day ($P = 0.001$) [59]. In a single-centre study following a similar protocol but 10 days' observation, the median time to fourth seizure was 6.26 days for the felbamate group and 2.54 for the placebo group ($P = 0.041$) [58]. Both of these studies were proof of principle studies to demonstrate the effectiveness of felbamate in intractable patients. Some patients remained on other AEDs, and these designs were not intended to be used as models of monotherapy.

Two subsequent studies of felbamate monotherapy using an 'active placebo' consisting of low-dose valproic acid have formed the basis of its recommended use as the sole AED in refractory patients with partial-onset seizures [55,60]. Additional open-label studies have demonstrated the effectiveness of felbamate in drug-refractory partial epilepsy [61,62].

In studies conducted before the discovery of serious hepatic and haematological toxicity, retention rate on felbamate in a clinical setting was favourable, as it was in a post-marketing study in which 91 of 132 refractory patients had enough clinical efficacy and lack of side-effects to warrant continuance of felbamate for 3 months or more after initiation [63].

The efficacy of felbamate in the Lennox–Gastaut syndrome was evaluated in a double-blind add-on parallel study involving 73 patients, mostly in the paediatric age range [56]. Felbamate or placebo was added to standard AEDs for 70 days. The dosage of felbamate was titrated to a maximum of 45 mg/kg of body weight per day or 3600 mg/day, whichever was less. Patients treated with felbamate had a 34% decrease in the frequency of atonic seizures ($P = 0.01$) and a 19% decrease in the frequency of all seizures ($P = 0.002$). A 'quality of life' measure, the global evaluation score, was significantly higher in the felbamate group than in the placebo group [56]. The improvement that occurred in the double-blind study was sustained for at least 12 months in subsequent open-label follow-up studies [64]. Additional open-label studies have confirmed the effectiveness of felbamate in the Lennox–Gastaut syndrome [65].

In a practice advisory statement in the USA, felbamate was classified as showing class I evidence efficacy for partial seizures in adults as adjunctive and monotherapy, and Lennox–Gastaut syndrome as adjunctive therapy. Class III evidence was found for primary generalized tonic–clonic seizures, absence seizures and partial seizures in children [66].

Adverse effects

In animal models, felbamate showed little toxicity [67]. Studies of carcinogenicity after high doses demonstrated a statistically significant increase in hepatic cell adenomas in some rodents, and an increase in benign interstitial cell tumours of the testes in male rats [68]. No teratogenic effects have been found in reproductive or teratology studies in rats and rabbits [68]. No evidence for bone marrow or hepatic toxicity was observed in any of the preclinical studies.

In human studies, felbamate was better tolerated as monotherapy, adverse experiences being more common when felbamate was used with other AEDs [55]. The most common adverse effects of felbamate as monotherapy were anorexia, vomiting, insomnia,

nausea and headache. The most common adverse effects in polytherapy trials included anorexia, vomiting, insomnia, nausea, dizziness, somnolence and headache [68,69]. In data provided by Carter Wallace, in clinical testing 12% (120 of 977 adults) discontinued felbamate because of adverse effects. In order of increasing frequency greater than 1%, adverse effects leading to discontinuation included weight decrease (1.1%), rash (1.2%), nausea (1.4%), various neurological symptoms (1.4%), and anorexia (1.6%) or psychological symptoms (2.2%) [68]. In studies with children, 6% (22 of 357) had felbamate discontinued, with symptoms leading to its discontinuance similar to those seen in adults. In one post-marketing use study, felbamate was initiated in 132 persons with chronic, refractory epilepsy after its release. Three or more months after initiation, felbamate had been discontinued in 24 patients because of adverse effects. Gastrointestinal symptoms were the most common single reason given, and dermatitis occurred in four patients [63].

In the clinical trials leading to felbamate approval, there had been no significant changes in laboratory tests among patients on felbamate, specifically white cell blood count, haematocrit and serum glutamate oxaloacetate transaminase (aspartate aminotransferase). However, as felbamate came into wider use, reports of serious adverse events surfaced. Thrombocytopenia was described in one report [70]. Scattered cases of aplastic anaemia came to the attention of the FDA by mid-1994, and three cases were reported in July alone. This unexpectedly high rate in conjunction with increasing use led the FDA to issue a warning on 1 August 1994, stating that 'Physicians should prescribe this drug only if it is absolutely necessary'. Information collected for the September 1994 FDA advisory panel meeting indicated that there had been 25 cases of aplastic anaemia reported (24 in the USA and one in Spain) [71]. In addition, 11 cases of hepatitis with four deaths had been reported. As of May 1995, Carter Wallace had evidence of 31 domestic post-marketing reports of aplastic anaemia and 14 cases of hepatitis with eight deaths (Table 40.2).

A thorough review of aplastic anaemia cases was performed. Of the cases reported, 23 (74%) met all of the criteria of the International Agranulocytosis and Aplastic Anemia Study [72]. Felbamate was judged to be the only cause in three cases, and the most likely cause in 11, for a total of 14 cases. Using a denominator of 110 000 persons exposed, the 'most probable' incidence was calculated to be 127 per million (lower limit, 27; upper limit, 209), with the general population rate for aplastic anaemia being 2 per million [72].

Table 40.2 Haematological reactions reported for patients receiving felbamate as of September 1994.

Reaction	*n*	Serious	Died
Aplastic anaemia	25	25	6
Pancytopenia	15	14	3
Leucopenia	29	18	1
Thrombocytopenia	16	10	2
Anaemia	4	4	0
Two of the above	14	11	1

Patient history and demographics suggest several features that may identify the high-risk patient. A prior history of AED allergy or toxicity, especially rash, was observed in 52%; a history of prior cytopenia in 42%; and evidence of immune disease, especially lupus erythematosus, in 33%. A case-by-case review of patients who developed aplastic anaemia revealed that an underlying immunological disease process was observed 34 times more frequently than expected, and if two of the above three factors were present, the patient's relative risk for aplastic anaemia quadrupled (Table 40.3). Only three patients had all three factors – cytopenia, allergy and an immunological process – among the entire aplastic anaemia cases and control groups available to the drug's manufacturer (Wallace), and all three developed aplastic anaemia. Only one paediatric patient (aged 18 years) was diagnosed with aplastic anaemia, and she had a prior diagnosis of systemic lupus erythematosus [73].

Duration of therapy is also an important factor. Duration of therapy prior to aplastic anaemia ranged from 23 to 339 days (mean 173 days) [73]. No cases reported up to the time of the review occurred in persons treated for more than 1 year, although in one additional case subsequently reported, the patient had been on felbamate for 8 years [74].

A total of 18 cases of hepatic failure were reported in patients receiving felbamate prior to September 1994. Evaluation of these reports indicates that 78% were female, 50% were aged 17 years or older, and the mean time to presentation was 217 days (25–939 days). A panel of hepatologists met independently to review the data on these cases and concluded that only seven had a probable association with felbamate, whereas the others were complicated by status epilepticus, viral hepatitis, shock liver or acetaminophen toxicity [73]. Using all reported cases of hepatic failure, the estimated incidence would be 164 per million, but using the numerator of seven, the incidence of hepatic failure would be estimated at 64 per million, or a risk estimate for hepatic failure of 1 per 18 500–25 000 exposures. Statistics regarding valproic acid reported hepatic-related fatality estimates of one case in 10 000–49 000 for the combined population, and 1 in 500–800 cases in high-risk young children under the age of 2 years receiving valproic acid polypharmacy [75]. These data suggest that the hepatotoxicity associated with felbamate is in the general range seen with valproic acid [73]. However, the age range differs markedly, with felbamate safer in the paediatric population but worse in adults, with just the opposite for

Table 40.3 Associated conditions in persons developing aplastic anaemia while on felbamate. A review of the 25 cases analysed by September 1994.

Previous history of bone marrow suppression	3
Previous history of blood dyscrasias	10
Previous history of drug allergy (not AEDs)	6
Previous history of autoimmune disease	5
Previous history of AED allergy	3
Current phenytoin use	16
Current clinical toxicity	3
Mental retardation	9
Taking drugs (not AEDs) associated with aplastic anaemia	12

AED, antiepileptic drug.

valproic acid. For both felbamate-induced aplastic anaemia and hepatotoxicity, females are at much greater risk (67% and 78%, respectively).

Felbamate is excreted in the urine and one case of urolithiasis with a felbamate stone in a 15-year-old boy has been reported [76]. One case of crystalluria and renal failure in an intentional overdose case with serum felbamate concentrations of 200 mg/mL has been observed [77]. Toxic epidermal necrolysis after initiation of felbamate has also been reported [78].

Place in current therapy

Update on risk to benefit ratio and indications

Although felbamate has been approved by the FDA for more than 15 years, a relative paucity of information exists about its clinical use. The most up-to-date review on the felbamate literature is described in a 2006 expert panel consensus on the use of felbamate [74]. New exposures to felbamate are estimated at between 3200 and 4200 patients annually; over the past 10 years, approximately 35 000 patients have been started on felbamate. Since 1994, one case of aplastic anaemia has been reported, which was described in 2000 in a 42-year-old woman who had been taking felbamate for 8 years and had a prior history of melanoma. One case of thrombocytopenia in a 14-year-old girl was reported in 2007. Felbamate was discontinued, thrombocytopenia resolved completely, but 4 months later aplastic anaemia occurred, thought to be unrelated to felbamate. Two cases of liver failure (one in 1995 and one in 1996) have been reported in felbamate patients since 1994; one was related to status epilepticus and the other was thought to be secondary to felbamate use.

Additional information has become available on the long-term effects of felbamate exposure. A prospective database affiliated with an epilepsy centre identified 77 long-term users of felbamate (data collected between 1986 and 2006) [62]. Laboratory and clinical outcomes are described in these patients, with an average treatment time of 7.5 years and a longest treatment time of 20 years. The study demonstrated significant weight loss in the first year of felbamate use, but weight loss was not sustained over long-term use. Significant reductions were noted in generalized tonic–clonic seizures and simple partial seizures. No clinically significant changes in laboratory parameters pertinent to liver or bone marrow function were seen; these results support the concept that the most serious felbamate adverse reactions are idiosyncratic [62].

Based on the 2006 expert panel consensus [74], felbamate should be regarded as a highly efficacious AED in patients refractory to first-line agents. Patients considered unsuitable candidates for felbamate include patients with new-onset epilepsy and patients with a history of adverse haematological events, hepatic dysfunction, autoimmune disease or a strong family history of autoimmune disease. The expert panel concluded that felbamate appears to have a risk–benefit ratio that allows it to be used in selected patients with refractory epilepsy. A similar conclusion was reached in 1999 by a joint American Academy of Neurology and American Epilepsy Society practice advisory [66].

Dosing recommendations

In adults, felbamate can be initiated at 1200 mg/day in three or four divided doses, with increases to 2400 and 3600 mg/day in weekly or biweekly increments of 600 or 1200 mg, as tolerated, as outpatients. In inpatient settings, felbamate can be titrated over a few days, especially if the other AEDs have been, or are being, eliminated or reduced [54]. In the outpatient environment, the doses of other AEDs should be reduced, generally by 20–33% upon initiation, and by further reductions as felbamate dose is increased. Most adverse effects can be eliminated by reducing doses of concomitant AEDs, especially if the goal is to attain monotherapy with felbamate. Some patients have tolerated doses as high as 7200 mg/day as monotherapy. A useful method to determine more precise doses for titrating patients is to start at approximately 20 mg/kg and increase to 40 mg/kg and then 50 mg/kg, 60 mg/kg or higher as needed.

Initiating felbamate in the presence of other AEDs can be difficult because of the drug interactions and propensity to develop adverse effects attributable to a greater total burden of AEDs. Nevertheless, careful attention to the general principle of reducing other AEDs vigorously in the presence of adverse effects, and increasing felbamate doses if levels have not exceeded 60 μg/mL, will permit patients to have an adequate exposure to this drug. In a patient with refractory epilepsy with particularly intense seizures or a propensity for status epilepticus, it may be best to err on the side of less aggressive concomitant AED adjustments initially rather than to decrease concomitant AEDs, as the patient develops signs and symptoms of concentration-related toxicity. In studies of adults, doses have ranged from 1800 to 4800 mg/day.

In children, recommended starting doses have been 15 mg/kg/day with weekly incremental increases to 45 mg/kg/day. Again, concomitant AEDs should be reduced by 20% or more upon initiation and reduced further as symptoms and blood levels indicate. It may be expected that doses for children may be larger than those for adults, and in our experience we have used doses of up to 80 mg/kg.

Felbamate is available as 400-mg tablets (scored, yellow, capsule shaped) useful for children; 600-mg tablets (peach-coloured scored, capsule shaped) and suspension (600 mg per 5 mL).

Laboratory and clinical monitoring

The FDA and Carter Wallace recommend full haematological evaluations prior to initiation of felbamate therapy, frequently during therapy and for a significant period of time after discontinuation of felbamate. Liver function tests are recommended every 1–2 weeks while on felbamate. It is not at all certain, however, that routine monitoring of haematological and hepatic parameters will be effective in detecting reactions. More important than laboratory testing is a careful review of the medical history and the avoidance of use of felbamate in patients who have a high-risk profile. Patients on felbamate should be taught the warning signs of aplastic anaemia and liver toxicity, and should have complete biochemistry and haematology tests done whenever any of these appear. These signs and symptoms include severe lethargy, nausea and vomiting, flu-like symptoms, easy bruising and unusual bleeding.

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41 Gabapentin

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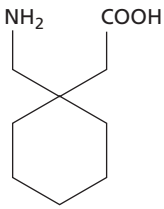

Primary indications	Adjunctive therapy or monotherapy of partial or secondary generalized seizures
Usual preparation	Capsules: 100, 300, 400 mg Tablets: 600, 800 mg Oral solution: 250 mg/5 mL
Usual dosages	Initial: 300–900 mg/day. Maintenance: 900–3600 mg/day
Dosing frequency	2 or 3 times/day
Significant drug interactions	Antacids containing aluminium or magnesium hydroxide can reduce gabapentin absorption by about 20%
Serum level monitoring	Not routinely used. Dosage is generally adjusted on the basis of clinical response
Reference range	2–20 mg/L
Common/important adverse effects	Drowsiness, dizziness, ataxia, headache, tremor, diplopia, nausea, vomiting, rhinitis, non-pitting leg oedema, weight gain
Main advantages	Good tolerability and lack of drug interactions
Main disadvantages	Modest efficacy, particularly in severe cases, and spectrum of efficacy restricted to partial epilepsies
Mechanism of action	Modulates neurotransmitter release by binding to the α_2-δ subunit of voltage-gated calcium channels. Additional actions are possible
Oral bioavailability	<65% (decreases with increasing dose)
Time to peak levels	2–3 h
Elimination	Renal excretion in unchanged form
Volume of distribution	0.65–1.04 L/kg
Elimination half-life	5–9 h
Plasma clearance	1.3–1.6 mL/kg/min (after intravenous dosing in non-elderly adults)
Protein binding	Nil
Active metabolites	None
Comment	A well-tolerated drug, the value of which is limited by relatively modest efficacy

Introduction

Gabapentin (1-aminomethyl-cyclohexyl-acetic acid, Neurontin®) is an amino acid derived by the addition of a cyclohexyl group to the backbone of γ-aminobutyric acid (GABA). It was originally synthesized in the 1970s in Freiburg, Germany, at the pharmaceutical company Goedecke A.G., part of Warner-Lambert, which has since been incorporated into Pfizer [1]. The rationale for its development was that the cyclohexyl group would make the inhibitory neurotransmitter GABA more lipophilic, thus helping it penetrate the CNS while maintaining similar pharmacology [2]. At this time, it was believed that gabapentin would act via GABA receptors in

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a similar manner to baclofen. However, subsequent studies have shown that gabapentin does not act *in vitro* at GABA receptors, but binds a subunit of voltage-sensitive calcium channels.

A US patent was granted in 1977 for the compound and its use in epilepsy. Following clinical trials, FDA approval was granted on 31 December 1993, and although originally available to clinicians as Neurontin® (Pfizer), it is now off patent and a large number of generic versions are available.

Chemistry

Gabapentin is a highly water-soluble bitter-tasting white crystalline substance with a molecular weight of 171.34 (conversion factor 1 μg/mL = 5.84 μmol/L). At 25°C it has two pK_a values at 3.68 and 10.70, and at physiological pH it is a zwitterion – an electrically neutral compound that carries both positive and negative charges on different atoms [3]. This permits absorption from the gut via the L-type amino acid transporter system, which usually carries L-leucine and L-phenylalanine [4].

Pharmacology

Activity in experimental models

There have been many studies of the effect of gabapentin in animal seizure models, with some correspondence to results from subsequent clinical experience (reviewed in ref. 3). Prevention of hind limb extensor response in rats in the maximum electroshock model has been a standard method to identify compounds with the potential to treat generalized tonic–clonic and partial seizures. In this model, gabapentin (ED_{50} = 9.1 mg/kg oral and 2.1 mg/kg intravenous) was found to be about as effective as phenytoin (ED_{50} = 9.5 mg/kg oral). In a partial-seizure model, the lowest effective dose of gabapentin required to block fully kindled hippocampal seizures in rats was 30 mg/kg, but the events were sometimes not completely blocked even with intraperitoneal doses up to 100 mg/kg. Gabapentin was found to be ineffective at preventing flash-induced myoclonic seizures in the photosensitive baboon (*Papio papio*).

Evidence of the non-epileptic uses of gabapentin has been available from animal studies for over a decade (reviewed in ref. 5). Gabapentin has anxiolytic-like effects and can prevent the nociceptive responses from hyperalgesia [6].

Mechanisms of action

Gabapentin was originally synthesized as a derivative of GABA, but whether its actions include a modification of GABAergic transmission is unclear. Whilst some authors have reported that gabapentin acts as a subtype-selective $GABA_B$ receptor agonist *in vitro* [7,8], other groups have not found this [9] and the actions of gabapentin appear not to be affected by $GABA_B$ receptor antagonists or agonists [10]. Although gabapentin has also been reported to elevate whole brain GABA levels in healthy volunteers, both acutely and after 1 month of therapy [11], the majority of evidence suggests that its pharmacology is not related to GABA neurotransmission or metabolism.

The identity of a protein in the brain to which gabapentin appears to bind specifically was discovered in 1996 by column fractionation of pig brain membranes which had been treated with [^{3}H]gabapentin. Fractions that retained radiolabelled gabapentin-binding activity were isolated and sequenced, demonstrating that gabapentin bound a protein which matched the α_2-δ type 1 subunit of voltage-gated calcium channels [12]. This binding site was shown to be present in high density in both brain and skeletal muscle. Subsequently, new α_2-δ subunit genes have been discovered, but it appears that [^{3}H]gabapentin binds only α_2-δ-1 and -2 [13].

Many reports have suggested that gabapentin reduces the cellular influx of calcium via voltage-gated calcium channels, identified by study of synaptosome fractions prepared from brain tissue or by electrophysiological techniques. However, not all researchers have found this, perhaps relating to strain differences in the mice used for the research [2,10]. There are also several studies suggesting that gabapentin, and the closely related compound pregabalin, subtly reduces the release of a wide variety of neurotransmitters including noradrenaline, glutamate, acetylcholine, substance P and calcitonin gene-related peptide, as reviewed recently [10]. The connection between gabapentin binding of the α_2-δ subunit, modulation of calcium currents, the reduction of neurotransmitter release and the subsequent clinical effects on seizures or pain remains to be clarified.

Pharmacokinetics

Absorption

Gabapentin is absorbed from the gastrointestinal tract through an active transport system, the efficiency of which decreases and becomes saturated at higher doses [10]. Absorption and bioavailability of gabapentin vary between patients, such that different doses may be required for therapeutic effect [14]. Peak serum concentrations are attained in 2–3 h. The oral bioavailability of gabapentin is about 60% after a 300-mg dose, but only around 40% following a 600-mg dose and about 35% at a steady-state dose of 1600 mg three times per day [15]. Interestingly, with doses above 3600 mg/day, there appears to be significantly increased oral bioavailability by using four rather than three doses per day [16]. This, of course, must be weighed against the inconvenience of such frequent dosing.

Since the half-life of gabapentin is fairly short (little more than 5 h [17]) it takes only 1–2 days before steady state is achieved with repetitive dosing [3]. Because of dose-dependent bioavailability, the relationship between serum gabapentin concentration and dose is non-linear, with less than proportional increases in serum levels when dosage is increased.

Distribution

Gabapentin has minimal or no binding to plasma proteins [15] and it has a volume of distribution of approximately 60 L, or 0.65–1.04 L/kg [3]. Gabapentin readily crosses the blood–brain barrier via the L-amino acid transport system, which, in animals, appears to be saturable [18]. The concentration found in human cerebrospinal fluid (CSF) is approximately 7–35% of that in plasma [19], with CSF levels continuing to rise for hours after peak plasma levels are achieved.

Elimination

Although in the dog there is considerable formation of *N*-methylgabapentin, no biotransformation of gabapentin has been observed in man [15]. In humans, gabapentin is excreted unchanged in the urine, and has an elimination half-life of 5–9 h in patients with normal renal function [20]. There is no significant effect of gender, but a significant linear decrease in clearance has been observed in patients between the age of 20 and 78 years [21].

The relatively slow absorption of gabapentin from the gut implies that fluctuations in serum drug concentrations at steady state are less marked than expected on the basis of the short half-life [22,23]. This, and the fact that accumulation of gabapentin in the central nervous system (CNS) continues beyond attainment of maximum serum concentrations, may explain its clinical efficacy when administered either two or three times per day [23].

Pharmacokinetics in special groups

Clearance is fastest in young children, and those from 1 month to 5 years of age require approximately 30% higher dosing rates than children aged 5–12 years old [24,25]. In 48 healthy children aged between 1 month and 12 years, peak plasma concentrations occurred 2–3 h after administration [24]. An Italian group [26] studied gabapentin plasma concentrations in a group of 41 patients with refractory epilepsy and confirmed that children may require larger doses of gabapentin than adults to achieve comparable drug plasma concentrations. At the other extreme of age, in the elderly, plasma gabapentin concentrations are higher than in non-elderly adults taking the same dose, presumably due to an ageing-related decrease in renal function [21].

Little is known of the pharmacokinetics of gabapentin in pregnancy. Ohman and colleagues [27] reported on the pharmacokinetics of gabapentin at delivery, and during the neonatal period and lactation. They reported drug accumulation in the fetus, possibly due to function of the L-type amino acid transporter system in the placenta. Transfer of gabapentin to breast milk was found to be extensive, but plasma levels in the breastfed newborn were low (12% of the mother's plasma level). In the newborn period there seemed to be a lower capacity to eliminate gabapentin than in adults.

The elimination half-life of gabapentin is prolonged with renal failure, and the clearance of the drug has been found to be proportional to creatinine clearance [3,20]. Tables to guide dosage in renal impairment are included in the product information sheet.

Drug interactions

There are no interactions between gabapentin and hepatically cleared medications since gabapentin is not metabolized in the liver and does not induce or inhibit cytochrome P450 drug-metabolizing enzyme systems or uridinediphosphoglucuronyl transferase isoenzymes. To date, no significant interactions have been reported between gabapentin and other antiepileptic medications. There is no interaction with a contraceptive regimen of norethindrone acetate and ethinylestradiol [28].

Antacids containing aluminium or magnesium hydroxide can reduce gabapentin absorption by about 20% [3,29], so it is recommended that administration of antacids and gabapentin should be separated by at least 2 h.

Serum level monitoring

Gabapentin should be titrated according to clinical effect. It is generally not helpful to monitor the serum levels of gabapentin, although in difficult individual cases an argument could be made for measurement to document 'therapeutic' drug levels and confirm compliance, or to document that high levels are ineffective [30].

The reference range has been estimated at approximately 2–20 mg/L, a figure derived from the trials of patients treated with therapeutic doses. There is evidence that serum drug concentrations below 2 mg/L are less likely to be effective [31]. Case reports suggest the development of tremor and mild changes in cognition with much higher serum levels (up to 85 mg/L) but a lack of serious toxicity even in overdose [32,33].

Efficacy

The efficacy of gabapentin has been subject to a number of recent reviews [34–36]. It should be highlighted that the dose of gabapentin used in many early trials was relatively low (up to 1800 mg/day), and efficacy may be improved by higher doses up to, and in some cases exceeding, 3600 mg/day [30].

Gabapentin as adjunctive therapy in epilepsy

Refractory partial seizures in adults

There have been four randomized placebo-controlled trials providing class I evidence of the efficacy of gabapentin as adjunctive therapy in adults with refractory partial-onset seizures [31,37–39] (Table 41.1). Each had a treatment phase of approximately 3 months' duration. Overall, these trials indicated that with daily doses of 1200–1800 mg, 23–33% of patients showed a more than 50% reduction in seizure frequency compared with baseline. The discontinuation rate of gabapentin because of adverse events ranged between 3% and 11.5%. In the four placebo-controlled trials, higher doses yielded higher responder rates.

The Study of Titration to Effect Profile of Safety (STEPS) trial used open-label gabapentin as adjunctive treatment in 2216 patients with partial epilepsy, with doses up to 3600 mg/day [40]. An increase was noted in the cumulative percentage of responders and of seizure-free patients as dose increased. In addition, a small observational study of 50 patients provides some evidence of additional benefit with very high doses of gabapentin (up to 6000 mg/day) [41].

Refractory partial seizures in children

Class I evidence of the efficacy of gabapentin as add-on treatment for intractable partial seizures comes from a multicentre double-blind placebo-controlled study of 247 children aged 3–12 years [42]. Gabapentin was titrated to a dose of 23–35 mg/kg/day. Children taking gabapentin had a median reduction in frequency of complex partial seizures of 35% (versus a 12% reduction on placebo), and a reduction in frequency of secondary generalized seizures of 28% (versus a 13% increase on placebo).

The efficacy of gabapentin adjunctive therapy for partial seizures in very young children has been assessed in a study of 76

Table 41.1 Summary of randomized placebo-controlled controlled trials of gabapentin as adjunctive therapy in adults with refractory partial seizures.

	Number of evaluable patients (total)	Number of patients and dose of gabapentin		Responder rate (%)	Median decrease in seizure frequency (%)	Discontinuation rate (%)
		n, evaluable	Daily dose (mg)			
UK gabapentin study [37]	113 (127)	52	1200	25 ($P = 0.04$)	29.2	12
		61	Placebo	9.8	12.5	6
Sivenius *et al*. [31]	43 (45)	9	1200	33	57 ($P = 0.02$)	Not reported
		16	900	12.5	25	
		18	Placebo	16.7	16.7	
US gabapentin study [38]	288 (306)	53	1800	26.4 ($P = 0.01$)	31.9	4
		91	1200	17.6 (NS)	20.0	2
		49	600	18.4 (NS)	24.3	6
		95	Placebo	8.4	5.9	1
Anhut *et al.* [39]	245 (272)	50	1200	28 ($P = 0.01$)	17.8	4
		94	900	22.9 ($P = 0.02$)	21.8	8
		96	Placebo	10.1	0.3	4

Responder rate = percentage of patients with at least 50% reduction in seizure frequency from baseline to treatment. Responder rate and median decrease in seizure frequency are calculated from the total number of evaluable patients after exclusions. *P*-values are reported where available.
NS, not significant

patients aged between 1 and 36 months [43]. Partial seizures were diagnosed either by electroencephalographic capture of a focal seizure, or by matching clinical semiology to a focal abnormality on EEG or brain imaging. A 40 mg/kg/day dose of gabapentin (intended to be equivalent to 30 mg/kg/day in older children and 1200 mg/day in adults) was compared with placebo. The rate of partial seizures was calculated by a blinded observer during 48 h of video-electroencephalography performed at baseline, and 72 h during the double-blind phase. Gabapentin was well tolerated, but although there was a slight effect on seizure frequency in favour of gabapentin, the result was not significant.

Primary generalized seizures

A double-blind placebo-controlled trial of 129 patients aged 12 years and over assessed the potential value of gabapentin as add-on treatment of refractory generalized seizures in patients with idiopathic or symptomatic generalized epilepsies [44]. Patients were randomized to receive either placebo or gabapentin 1200 mg/day in addition to their usual medication. Although an intention-to-treat and evaluable-patient analysis both showed that gabapentin caused greater reduction in the frequency of generalized tonic–clonic seizures than placebo, the result did not reach significance. This may reflect the low dose of gabapentin chosen. No effect was seen on absence or myoclonic seizures. Results in the subgroup of children included in this study were not reported separately.

Gabapentin as monotherapy in epilepsy

Conversion to monotherapy in patients with refractory partial seizures

In a randomized double-blind study, 275 patients with complex partial or secondary generalized seizures were randomized to receive 600, 1200 or 2400 mg/day gabapentin [45] and then underwent a gradual withdrawal of their baseline antiepileptic drug (AED) therapy. If seizure deterioration occurred during the withdrawal phase, patients were required to exit the study. There was no dose–response relationship in outcome measures including time to exit, completion rate and mean time on monotherapy. Overall, completion rate was only 20%, perhaps reflecting the difficulty in converting from polytherapy to monotherapy. Completion rates were higher among patients who had discontinued one AED (23%) than two AEDs (14%), and higher among patients who were not withdrawn from carbamazepine (27%) than among those who were (16%).

Short-term presurgical assessment in patients with refractory partial seizures

An inpatient double-blind study conducted in the USA compared a daily gabapentin dose of 300 mg versus 3600 mg in 82 patients, all of whom had their usual medication stopped for inpatient recording of their seizures [46]. The outcome variable was median time to exit (due to defined seizure-related endpoints or adverse events) in the course of an 8-day period, which was found to be significantly longer for the higher dose of gabapentin (151 h versus 85 h).

Studies in patients with predominantly newly diagnosed partial seizures

A randomized trial compared outcome in 218 patients treated with gabapentin monotherapy for newly diagnosed partial seizures (300, 900, 1800 mg/day) and 74 patients treated with 600 mg/day carbamazepine [47]. The allocation to carbamazepine or gabapentin was not blinded but the dose of gabapentin was double blind. Patients were required to exit if they experienced three simple or complex partial seizures, one generalized tonic–clonic seizure or status epilepticus. In addition, patients could be withdrawn for lack of efficacy, adverse events or non-compliance. Completion rate was 37% in the carbamazepine group versus 25%, 39% and 38% in the gabapentin groups at 300, 900 and 1800 mg/day respectively.

Although the completion rates for 900 and 1800 mg/day of gabapentin were similar to that of carbamazepine, more patients exited from the gabapentin arms due to seizures (40% and 43% respectively) than from the carbamazepine arm (30%), but more patients withdrew due to adverse events while taking carbamazepine (24%) than gabapentin (4% and 14%).

A subsequent double-blind, randomized, multicentre study of gabapentin versus lamotrigine monotherapy was completed in 309 patients with newly diagnosed partial and/or generalized tonic–clonic seizures [48]. Gabapentin was maintained at 1200–3600 mg/day, and lamotrigine at 100–300 mg/day. Overall, 72% of the gabapentin group and 67% of the lamotrigine group completed the 30-week study, and 76% of patients in both groups were seizure free for the final 12 weeks of treatment, a period shorter than desirable in assessing efficacy in newly diagnosed patients. The number of patients with primarily generalized tonic–clonic seizures in this study was too small for a meaningful subgroup analysis. However, it is of interest that five (16.1%) of the 31 patients with primarily generalized tonic–clonic seizures randomized to gabapentin met exit criteria, while none of the 27 patients with primarily generalized tonic–clonic seizures randomized to lamotrigine met exit criteria.

The recently completed SANAD trial in the UK compared gabapentin with carbamazepine, oxcarbazepine, topiramate and lamotrigine in 1791 patients with mostly (89%) partial epilepsy for whom carbamazepine was considered a preferable choice to valproate [49]. This randomized open-label trial included predominantly (82%) newly diagnosed patients, although patients who had been given earlier suboptimal treatment or had relapsed after withdrawal of effective therapy were not excluded. The study showed that time to treatment failure (defined as stopping the randomly assigned drug due to inadequate seizure control or intolerable side-effects, or the addition of other AEDs) was significantly better with lamotrigine than with gabapentin [hazard ratio 0.65; 95% confidence interval (CI) 0.52–0.80] when prescribed at the usual dose used by the clinician [49]. For the other primary outcome measure, time to 12-month remission, carbamazepine was significantly better than gabapentin [hazard ratio 0.75 (0.63–0.90)].

Newly diagnosed absence seizures

A total of 33 children aged 4–12 years with newly diagnosed absence epilepsy were included in two identical, double-blind, placebo-controlled trials, in which gabapentin was tested at doses of 9.7–19.1 mg/kg/day [50]. A 2-week double-blind treatment phase was followed by a 6-week open-label phase. Gabapentin did not significantly decrease or increase seizure frequency (derived from quantified EEGs) compared with placebo in this study, although the lack of efficacy may relate to the relatively low doses used.

Gabapentin in non-epilepsy indications

Gabapentin has efficacy in a number of non-epilepsy indications (reviewed in ref. 50). In particular, it has shown efficacy in neuropathic pain, particularly postherpetic neuralgia [52] and diabetic neuropathy [53]. It has also been useful in trigeminal neuralgia. The Cochrane group has analysed 15 studies of the use of gabapentin in acute, chronic or cancer pain, including a total of 1468 patients [54]. In chronic pain, the number needed to treat (NNT) was 4.3 (95% CI 3.5–5.7), whereas it was 3.9 in postherpetic neuralgia and 2.9 in diabetic neuropathy. In addition, there are reports that gabapentin may be useful in movement disorders, migraine prophylaxis, perioperative pain and cocaine dependence.

Adverse effects

General overview of the most common adverse effects

The adverse effects of gabapentin tend to be CNS related, mild to moderate in severity, and present primarily in the first 2–3 weeks of treatment [30]. A review of adverse events reported in 1748 patients treated in early trials confirmed the good tolerability of this agent [55] (Table 41.2). Overall, only 7.4% of patients treated with gabapentin withdrew due to an adverse event compared with 3.3% of 485 patients taking at least one AED but prescribed placebo rather than gabapentin. The most common adverse events were somnolence and dizziness.

An open-label French study investigated the use of gabapentin as an add-on drug in 610 patients with partial epilepsy [56]. There was little difference in tolerability when gabapentin was used at doses between 900 and 2400 mg/day. The most common adverse effects were (in decreasing order of incidence) somnolence, asthenia, weight gain, nausea, ataxia and vertigo. A tolerability analysis from the STEPS trial, an open-label study of gabapentin as adjunctive therapy for partial seizures, showed good tolerability up to doses of 3600 mg/day, but beyond that dose there were too few patients to draw meaningful conclusions [57].

A number of studies permit an assessment of tolerability as a function of the starting dose and rate of titration. In a randomized controlled trial of 574 patients with partial seizures, gabapentin initiation at 900 mg/day was more likely to cause dizziness than

Table 41.2 Summary of the adverse events reported in 1748 patients treated with gabapentin in early trials.

Number (%) of patients with one or more adverse events	Controlled studies		All studies
	Placebo (n = 307)	Gabapentin (n = 485)	Gabapentin (n = 1160)
	174 (56.7)	369 (76.1)	944 (81.1)
Adverse events			
Somnolence	30 (9.8)	98 (20.2)	283 (24.4)
Dizziness	24 (7.8)	87 (17.9)	235 (20.3)
Ataxia	16 (5.2)	64 (13.2)	202 (17.4)
Fatigue	15 (4.9)	54 (11.1)	171 (14.7)
Nystagmus	15 (4.9)	45 (9.3)	174 (15.0)
Headache	28 (9.1)	42 (8.7)	176 (15.2)
Tremor	12 (3.9)	35 (7.2)	174 (15.0)
Diplopia	6 (2.0)	31 (6.4)	124 (10.7)
Nausea and/or vomiting	23 (7.5)	29 (6.0)	108 (9.3)
Rhinitis	12 (3.0)	22 (4.5)	101 (8.7)

From ref. 55 with permission.

a 3-day dose titration (10.5% versus 6.4% respectively) [58]. However, there was no significant difference in the incidence of fatigue, ataxia or somnolence, suggesting that rapid initiation is generally well tolerated. It should be stressed that high starting doses of gabapentin are certainly feasible in the acute situation, and starting doses up to 3600 mg/day have been tolerated in some double-blind multicentre trials. In one such study, adverse events were reported in a higher proportion of patients treated with an initial daily dose of 3600 mg than with 300 mg (73% versus 52%), but most of these were of mild to moderate intensity, and the duration of adverse events was shorter in patients receiving the higher dose (mean duration 28 h versus 39 h in those treated with 300 mg/day) [46].

Randomized add-on placebo-controlled clinical trials have shown that increases in partial seizure frequency of at least 50% or at least 75% are *no more* likely with gabapentin than with placebo [37,39]. There are, however, several reports of seizure aggravation by gabapentin, mostly in patients with generalized epilepsies. Most are anecdotal, unquantified and do not involve rechallenge. In one of the most comprehensive reports, based on a review of clinic charts of 104 consecutive patients started on add-on gabapentin, there were 13 cases of subtle myoclonus, which was multifocal in 10 and focal (contralateral to the epileptic focus) in three [59]. Six patients had a severe chronic static encephalopathy, while five had no diagnosis other than seizures. Two patients had an exacerbation of pre-existent myoclonus. An EEG recorded during myoclonus in three patients showed no correlate. Withdrawal of gabapentin resulted in rapid cessation of the myoclonus, although discontinuation of therapy was not deemed necessary in most cases. Patients with renal failure appear to be at special risk of developing a more disabling myoclonus [60].

Less common adverse effects of gabapentin include diplopia, tremor, dystonia, rhinitis and non-pitting leg oedema.

Serious, rare and long-term effects

Serious idiosyncratic reactions with gabapentin are extremely uncommon, and gabapentin has a much lower potential to cause hypersensitivity reactions than many other AEDs, such as carbamazepine and lamotrigine [61].

Prescription event monitoring of 3100 patients in the UK (136 of whom were children) found no previously unrecognized adverse events [62]. Two cases of hyponatraemia were possibly related to gabapentin, three cases of hair loss were reported after at least 6 months' treatment, and there were 17 cases of overdose recorded. A review of serious, rare or long-term adverse events concluded that oedema and myoclonic jerking might be a consequence of high doses of gabapentin, hyponatraemia might be a rare event and hair loss could be a long-term effect of gabapentin treatment. Although cancers and infections were observed in a few patients, they were not positively linked to gabapentin.

A case of rhabdomyolysis considered to be caused by gabapentin in an elderly woman with neuropathic pain was recently reported [63].

Use in pregnancy

Published data from the prospective UK Epilepsy and Pregnancy Register include 31 pregnancies in which the mother was exposed to gabapentin monotherapy. Only one major congenital malformation (a ventricular septal defect) was detected [64]. The Neurontin Pregnancy Registry, which included both prospective and retrospective data, reported no malformations in babies born of 11 mothers taking gabapentin monotherapy throughout pregnancy [65]. In another study, no congenital anomalies were reported in 11 births in which the fetus was exposed to gabapentin in the first trimester [66]. These data are insufficient to determine possible risks associated with gabapentin treatment in pregnancy.

Place in current therapy

Main indications

Gabapentin is effective in focal epilepsies but *may* aggravate generalized epilepsies. Gabapentin is widely perceived to be better tolerated than most other AEDs, but possesses relatively poor efficacy. This perception probably arises, at least in part, from the relatively low doses used in the pivotal clinical trials. Post-marketing open-label studies have demonstrated greater efficacy with higher doses.

A few studies have been performed to compare gabapentin with other AEDs, including carbamazepine [47,49], lamotrigine [48,49], oxcarbazepine [49] and topiramate [49]. Conclusions are limited by methodological issues. In the SANAD study [49], gabapentin was inferior to lamotrigine in time to treatment failure and to carbamazepine in time to 12-month remission.

In another study comparing gabapentin with carbamazepine, carbamazepine demonstrated superior efficacy, but at the expense of more frequent adverse events [47]. Compared with lamotrigine, gabapentin may show inferior effectiveness [49] but it has the advantage of lacking the potential for serious adverse effects, such as cutaneous hypersensitivity [48,49], and can be introduced much more rapidly.

In general, the main advantages of gabapentin are that it is safe and well tolerated, with lack of drug interactions and a wide therapeutic index. Rapid titration is generally well tolerated and is without significant risk of serious adverse effects. It may be an appropriate choice in patients who have demonstrated a low threshold for adverse effects with other AEDs, in those with hepatic failure or in patients in whom drug interactions may have serious consequences.

Gabapentin approval in most countries includes adjunctive and monotherapy use in partial seizures, as well as an indication for neuropathic pain.

Administration and dosage

The current Neurontin® US physician prescribing information states that the starting dose for patients older than 12 years is 300 mg three times per day [67]. In the elderly and in refractory patients on multiple drugs it is usual practice to introduce gabapentin at a slower rate to improve tolerability, for example starting at 300 mg/day and increasing to 600 then 900 mg/day at weeks 2 and 3 respectively. However, if a rapid response is required, starting doses up to 3600 mg/day can be well tolerated. The effective dose of Neurontin® is stated as 900–1800 mg/day, based on double-blind study data [67]. However, post-

marketing experience now supports better antiepileptic effects with higher doses, and many clinicians now routinely raise the dose to 3600 mg/day. There is limited evidence for use of higher doses.

In children 3 to 12 years old, the starting dose can be in the order of 10–15 mg/kg/day in three divided administrations, and may be increased over a period of approximately 3 days to the effective dosage, which is about 40 mg/kg/day in children aged 3 and 4 years, and 25–35 mg/kg/day in children 5–12 years of age. Dosages up to 50 mg/kg/day have been well tolerated.

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42 Lacosamide

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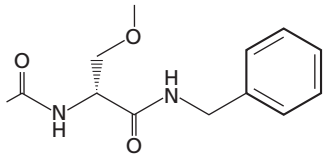

Primary indications	Adjunctive therapy of partial-onset seizures with or without secondary generalization in adults with epilepsy
Usual preparation	Tablets: 50 mg, 100 mg, 150 mg, 200 mg Syrup: 15 mg/mL Intravenous solution: 10 mg/mL
Usual dosages	Initial: 100 mg/day. Maintenance: 200–400 mg/day
Dosing frequency	2 times/day
Significant drug interactions	Population pharmacokinetic studies suggest that enzyme-inducing antiepileptic drugs reduce serum lacosamide levels by about 25%
Serum level monitoring	There is insufficient information on the value of monitoring serum lacosamide levels
Reference range	Not clearly defined
Common/important adverse effects (>10%)	Dizziness, headache, nausea, diplopia
Main advantages	Well-documented efficacy, lack of clinically important drug interactions and availability of an intravenous formulation
Main disadvantages	Limited clinical experience, nervous system and gastrointestinal adverse effects
Mechanism of action	Enhances slow inactivation of voltage-gated sodium channels; may interact with collapsin response mediator protein 2 (CRMP-2)
Oral bioavailability	~100%
Time to peak levels	0.5–4 h following oral dosing
Elimination	Partly by excretion in unchanged form in the urine (40% of the administered dose) and partly by metabolism (primarily O-demethylation) followed by excretion
Volume of distribution	0.5–0.8 L/kg
Elimination of half-life	12–16 h
Plasma clearance	No published data
Protein binding	<15%
Active metabolites	None
Comment	A potentially valuable antiepileptic drug, but more data are needed to establish its place in current therapy

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Introduction

Lacosamide [Vimpat® (SPM 927), formerly known as harkoseride] was specifically synthesized to act as an anticonvulsant, but additional pharmacological properties justifying its evaluation in other indications were subsequently discovered. Studies have been conducted in parallel in patients with epilepsy and in patients with neuropathic pain. Clinical trials completed to date in patients with epilepsy have used lacosamide as adjunctive therapy in refractory partial seizures, but potential usefulness in other epilepsy syndromes is also being investigated.

Lacosamide is unique among existing antiepileptic drugs (AEDs) in that it selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation. Another unique mechanism which may contribute to its efficacy in epilepsy and neuropathic pain relates to the potential interaction of lacosamide with collapsin response mediator protein 2 (CRMP-2).

Chemistry

Lacosamide is a functionalized amino acid and corresponds chemically to (*R*)-2-acetamido-*N*-benzyl-3-methoxypropionamide. Its chemical formula is $C_{13}H_{18}N_2O_3$. Lacosamide is a white to light-yellow crystalline powder with a molecular weight of 250.30. Its solubility in phosphate-buffered saline (pH 7.5, 25°C) is 20.1 mg/mL.

Pharmacology

Activity profile in experimental models of seizures and epilepsy

Lacosamide shows protective activity against seizures in a variety of experimental models, mostly in the dose range of 1–30 mg/kg intraperitoneally (i.p.) [1]. Models in which anticonvulsant activity has been demonstrated include audiogenic seizures in Frings mice, tonic extension seizures induced by maximal electroshock in mice and rats, and seizures induced by *N*-methyl-D-aspartate (NMDA) administration in mice. Activity has also been demonstrated in the 4-aminopyridine model of epileptiform bursting [2], the 6-Hz psychomotor seizure model of pharmacoresistant epilepsy in mice [1,3], the perforant path model of self-sustained status epilepticus in rats, and the hippocampal-kindled rat model [1,3,4]. Lacosamide effects in the kindling model are not limited to inhibition of kindled seizures, but include a delaying effect on amygdala-kindling acquisition [5].

Lacosamide is ineffective against the clonic seizures induced by pentylenetetrazole and the tonic–clonic seizures induced by picrotoxin and bicuculline in rats and mice. However, lacosamide does increase the threshold for minimal seizures induced by intravenous infusions of pentylenetetrazole in mice [1].

A possible neuroprotective activity of lacosamide against brain damage caused by a variety of experimental insults – including hippocampal damage caused by status epilepticus and infarct size in the rat middle cerebral artery occlusion model of ischemia – has been documented [6].

Activity in models relevant to non-epilepsy indications

Lacosamide is effective in various animal models of chronic pain [1,7].

Mechanisms of action

Enhanced slow inactivation of voltage-gated sodium channels

Unlike other drugs used to treat epilepsy and diabetic neuropathic pain, lacosamide selectively enhances slow inactivation of neuronal voltage-gated sodium channels without affecting fast inactivation (Table 42.1). Depending on the membrane potential and the neuronal activity, voltage-gated sodium channels are in different states. At the resting state, sodium channels are closed and can be opened by depolarization of the cell membrane, allowing sodium ions to enter the cell and thus leading to the initiation of an action potential. The open time of voltage-gated sodium channels is very short (a few milliseconds) and the channel rapidly enters the 'fast inactivated' state (pore occlusion by cytoplasmic domains) from which it cannot be activated. When the membrane potential returns to its baseline (action potential termination), the sodium channel returns to its resting state, from which it may be activated again. Under conditions of slightly prolonged depolarization and sustained neuronal firing activity, the sodium channel can enter the 'slow inactivated' state, which involves the collapse of the inner pore structure. This process happens at a relatively slower rate, taking 1 second to a minute and reduces the long-term availability of voltage-gated sodium channels. Drugs can either block the open channel (e.g. local anaesthetics), enhance fast inactivation (classical sodium channel-blocking AEDs such as carbamazepine or phenytoin) or enhance slow inactivation (lacosamide) [8].

Interaction with CRMP-2

Interaction with CRMP-2 was identified as a second possible mechanism of action for lacosamide. Follow-up experiments suggested a functional interaction of lacosamide with CRMP-2

Table 42.1 Inhibition of sodium current by lacosamide and other antiepileptic drugs with and without removal of fast inactivation.

	Lacosamide	Lamotrigine	Carbamazepine	Phenytoin
% Inhibition of Na^+ current with fast inactivation	32	50	71	48
% Inhibition of Na^+ current after removal of fast inactivation	29	12*	6*	1*

Availability of Na^+ channels was determined in neuroblastoma cells by a 10-msec test pulse to 0 mV from a holding potential of –60 mV. Fast inactivation was removed by a hyperpolarizing pulse to –100 mV (500 msec) prior to the 10-msec test pulse. Concentration of drug was 100 μM for all compounds. *$P < 0.05$ versus % inhibition with fast inactivation.
Data from ref. 1.

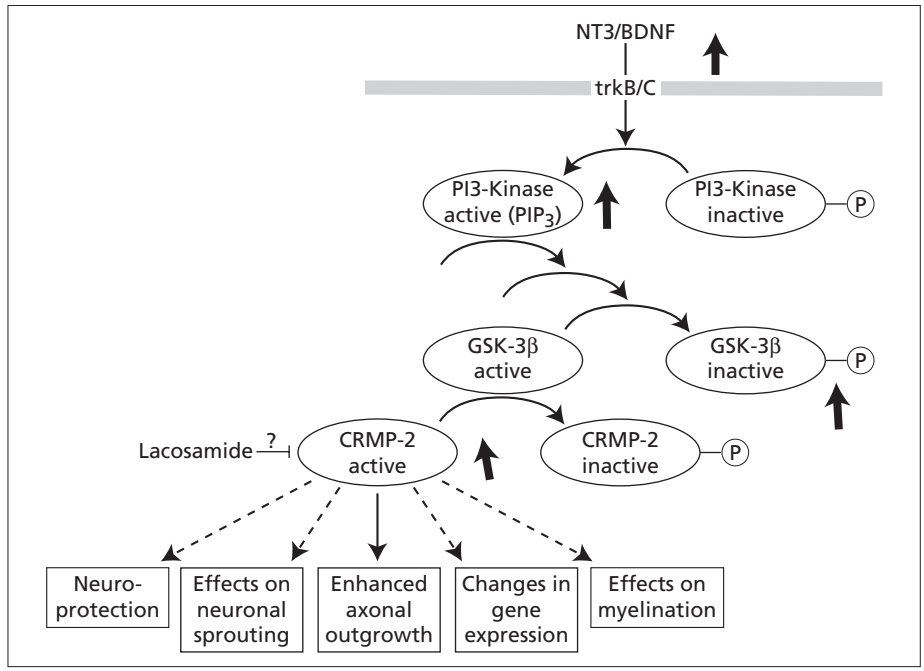

Fig. 42.1 The role of CRMP-2 in the signal transduction cascade of neutrophic factors. From ref. 1 with permission.

in vitro [1]. The confirmation of these initial findings, including more detailed pharmacological investigations, is ongoing.

Neurotrophins such as NT-3 (neurotrophin-3) and BDNF (brain-derived neurotrophic factor) activate their receptors in the plasma membrane, triggering a transduction cascade that regulates the activity of intracellular protein kinases (e.g. PI3 kinase or GSK-3β-glycogen synthase kinase), and results in increased levels of active CRMP-2. Active, non-phosphorylated CRMP-2 has been shown to enhance axonal outgrowth and might also be involved in the induction of other cellular responses (Fig. 42.1). Clinically, an interaction of lacosamide with CRMP-2 may prevent the formation of abnormal neuronal connections in the brain; however, the role of CRMP-2 interaction in seizure control has yet to be determined.

Brain-derived neurotrophic factor is also directly involved in the development of epilepsy [9,10] and neuropathic pain [11,12]. Lacosamide could interfere with these neurotrophin-induced processes and potentially attenuate the development and/or progression of epilepsy and/or neuropathic pain. Neuroprotective effects of lacosamide were observed *in vivo* in animal models, such as following status epilepticus. Bretin *et al*. [13] suggested recently that collapsin response mediator proteins, in addition to their role in neuronal morphogenesis, may contribute to neuronal plasticity. They specifically demonstrated that CRMP-2 is involved in the downregulation of the *N*-methyl-D-aspartate receptor subunit NR2B, a key modulator of pain transmission.

Further experiments to examine the possible interaction between lacosamide and CRMP-2, followed by appropriate clinical trials, should determine whether or not this novel mechanism of action can result in symptomatic and/or disease-modifying effects.

Pharmacokinetics

Key pharmacokinetic features

Lacosamide is rapidly and completely absorbed after oral administration, with negligible first-pass effect [14]. The oral bioavailability is approximately 100%. Peak plasma concentrations occur between 0.5 and 4 h post dose, or immediately following i.v. infusion (i.e. at the end of infusion) [14]. Plasma concentrations are proportional to dose, with low intra- and inter-subject variability. The influence of concomitant food intake on the bioavailability of lacosamide was evaluated in a food interaction study in which lacosamide was given as tablets (three tablets of 100 mg) after a high-fat breakfast or in a fasting state. The results of this study demonstrated that food has no influence on the pharmacokinetics of lacosamide [15].

When administered intravenously over 15 min, the parenteral formulation was shown to be bioequivalent to the tablet formulation with respect to area under the plasma concentration–time curve [$AUC_{(0-tz)}$] but not with respect to C_{max}, which slightly exceeded the upper boundary of the generally accepted bioequivalence range (0.8–1.25) [16]. Bioequivalence was demonstrated with respect to both C_{max} and AUC using 30- and 60-min infusion durations [17]. Bioequivalence has also been shown between two 100-mg tablets of lacosamide (200 mg) and a syrup containing lacosamide 200 mg (10 mg/mL) after oral single-dose administration in healthy subjects.

Lacosamide is negligibly (<15%) bound to plasma proteins and is distributed in total body water, with an apparent volume of distribution of about 0.5–0.8 L/kg.

The half-life of lacosamide is approximately 12–16 h and is not influenced by dose, route of administration (oral or intravenous) or duration of treatment (single versus multiple dosing) [14].

Following twice-daily dosing, steady-state plasma concentrations are achieved after 3 days [18].

Approximately 40% of orally administered lacosamide is excreted unchanged in the urine, and another 30% is recovered in the form of the inactive O-desmethyl-metabolite SPM 12809. SPM 12809 has no known pharmacological activity and its concentration in plasma amounts to approximately 10% of the plasma concentration of the parent compound. The cytochrome P450 isoenzyme CYP2C19 is involved in the formation of SPM 12809, since the plasma concentration of SPM 12809 is reduced in poor CYP2C19 metabolizers and in the presence of CYP2C19 inhibitors; however, the CYP2C19 genotype seems to have no major influence on plasma lacosamide concentrations [19].

Pharmacokinetics in special populations

There are limited data on the influence of age on lacosamide pharmacokinetics. In a study conducted in 23 subjects over 65 years of age (age range not stated), steady-state plasma lacosamide concentrations were 10–35% higher than those recorded in non-elderly adults [18], which may be due to differences in body weight as well as decreased renal function in the elderly.

Since renal excretion contributes significantly to the elimination of lacosamide and SPM 12809, exposure to the parent drug and to its main metabolite increases with increasing degree of renal impairment. Exposure to lacosamide, measured as area under the plasma concentration–time curve during a dosing interval at steady state [$AUC_{(0-\tau)ss}$], in subjects with mild or moderate renal impairment is increased by approximately 30% compared with healthy subjects. In subjects with severe renal impairment, an approximately 60% increase in exposure compared with healthy subjects is seen. Based on the described data, no dose adjustments should be necessary in subjects with mild and moderate impairment of renal function (CLcr >30 mL/min). Subjects with severe renal impairment (CLcr ≤30 mL/min) are expected to have a considerably higher exposure to lacosamide (approximately 60% higher) than subjects with normal renal function. Therefore, the lacosamide dose for subjects with severe and end-stage renal disease should not exceed 250–300 mg/day [20,21].

Lacosamide is cleared by haemodialysis. A dose supplement of up to 50% of the divided daily dose for patients following haemodialysis should be considered [20]. Subjects with hepatic impairment (Child–Pugh score B) showed approximately 50% higher systemic exposure to lacosamide in comparison with healthy subjects, which was attributed, in part, to reduced renal function in these patients. No dosage adjustment is thought to be needed in patients with mild to moderate hepatic insufficiency, but titration should proceed with caution [20]. Patients with severe hepatic impairment have not been studied.

Drug interactions

Overall, lacosamide exhibits a low drug–drug interaction potential, and no dose adjustment is necessary when lacosamide is coadministered with other drugs [22].

Effects of other drugs on lacosamide

In clinical pharmacology studies, concomitant treatment with carbamazepine 400 mg/day or valproic acid 600 mg/day had no influence on plasma lacosamide concentrations [14,19]; however, in a population pharmacokinetic study in subjects with partial-onset seizures, comedication with enzyme-inducing antiepileptic drugs (AEDs) (carbamazepine, phenytoin, phenobarbital) reduced lacosamide exposure by 25% [23].

Digoxin, metformin, omeprazole and a combined oral contraceptive were not found to influence to a clinically significant extent the pharmacokinetics of lacosamide [19].

Effect of lacosamide on other drugs

In human hepatocytes, lacosamide at 100 μM/L (25 μg/mL) showed no potential to induce or inhibit the activity of CYP isoforms 1A2, 2B6, 2C9 and 3A4, but *in vitro* inhibition of CYP2C19 by lacosamide was observed with an IC_{50} of 1797 μM [1]. In subsequent studies with the recombinant human enzymes CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5, lacosamide showed no or low inhibitory interactions, suggesting a low risk for inhibition of CYP isoforms *in vivo*. In clinical pharmacology studies, lacosamide plasma concentrations were comparable among both extensive and poor metabolizers of CYP2C19 [22].

In clinical studies, lacosamide was generally well tolerated when administered concomitantly with one to three AEDs. There was no indication that steady-state plasma concentrations of concomitant AEDs [e.g. levetiracetam, carbamazepine, carbamazepine-10,11-epoxide, lamotrigine, topiramate, the oxcarbazepine monohydroxy derivative (MHD), phenytoin, valproic acid, gabapentin and zonisamide] were affected by concomitant intake of lacosamide at any dose [22,24].

Multi-dose drug–drug interaction studies in healthy subjects showed that lacosamide 200 mg twice daily (b.i.d.) had no influence on the pharmacokinetics of digoxin and metformin [22]. Likewise, there was no influence of lacosamide 200 mg b.i.d. on the pharmacokinetics and hormonal effects of an oral contraceptive containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel in healthy subjects [19].

Serum level monitoring

There is insufficient information on the value of monitoring lacosamide plasma concentrations, and there is no indication that monitoring lacosamide plasma concentrations may help in individualizing therapy, except for compliance assessment.

Efficacy

Adjunctive treatment with lacosamide was evaluated in a number of phase II and III trials in adults with simple partial-onset seizures and/or complex partial-onset seizures, with or without secondary generalization. Both the oral and parenteral formulations were tested in clinical trials, although the i.v. formulation was studied for safety only. Lacosamide also underwent a parallel clinical development in patients with diabetic

neuropathic pain. Controlled clinical trials in patients with partial-onset seizures have been published or presented as abstracts [24–26].

A first phase II study was performed to define the maximum tolerated dose (MTD) of lacosamide by testing a dose range of 100 mg/day to 600 mg/day [27]. The median MTD for the sample was 300 mg/day, but approximately 50% of subjects had an MTD of 400–600 mg/day. Based on these findings, three lacosamide doses (200 mg, 400 mg and 600 mg/day) were selected for the pivotal trials. Lacosamide 600 mg/day is not an approved dose by either the European Medicines Agency (EMEA) or Food and Drug Administration (FDA).

Placebo-controlled trials in partial-onset seizures

The three randomized placebo-controlled clinical trials in epilepsy patients used a similar double-blind parallel-group design, which involved a titration period in which lacosamide was increased up to the target dose in 100 mg/day weekly increments, followed by a 12-week maintenance period. All three trials demonstrated the efficacy of adjunctive lacosamide therapy in adults with partial-onset seizures compared with placebo.

The primary objective of the first trial was to evaluate the efficacy and safety of lacosamide 200 mg/day, 400 mg/day and 600 mg/day administered on a b.i.d. schedule as adjunctive therapy in adults (18–65 years) with uncontrolled partial-onset seizures currently treated with one or two AEDs [24]. In order to be randomized in the trial, patients had to experience an average of at least four partial-onset seizures per 28 days during an 8-week prospective baseline. Following the baseline period, eligible patients were randomized in a 1:1:1:1 ratio to one of four treatment arms: placebo or lacosamide 200 mg/day (100 mg b.i.d.), 400 mg/day (200 mg b.i.d.) or 600 mg/day (300 mg b.i.d.). The titration period lasted 6 weeks and was followed by a 12-week maintenance period. A single backtitration by 100 mg was allowed at the end of the titration period for patients experiencing significant adverse events. A total of 418 patients were randomized in this trial. These patients were highly refractory as demonstrated by the fact that approximately 50% of patients had tried seven or more AEDs in their lifetime and that the median baseline seizure frequency across all treatment groups was 11 to 13 seizures per 28 days. The primary efficacy variable, median percent reduction in seizure frequency from baseline to maintenance, was 10% in the placebo group and 26%, 39% and 40% in the lacosamide 200 mg/day, 400 mg/day and 600 mg/day groups, respectively. Reductions in seizure frequency over placebo were significant for the lacosamide 400 mg/day (28.4%, $P = 0.0023$) and 600 mg/day (21.3%, $P = 0.0084$) groups. Although there was a statistical trend favouring the lacosamide 200 mg/day group, the median percent reduction in seizure frequency per 28 days over placebo did not reach statistical significance (14.6%, $P = 0.10$). A significant proportion of patients experienced a 50% or greater decrease in seizure frequency during the maintenance period when treated with lacosamide 400 mg/day (41.1%, $P = 0.0038$) and 600 mg/day (38.1%, $P = 0.0141$) compared with placebo (21.9%). A total of 32.7% of 200 mg/day lacosamide-treated patients had a 50% or greater decrease in seizure frequency during the maintenance period ($P = 0.0899$ compared with placebo).

The second placebo-controlled trial was conducted in 485 patients with refractory partial-onset seizures receiving up to three AEDs, and explored lacosamide doses of 200 and 400 mg/day [25]. Significant median percent reductions in seizure frequency of 35% and 36% for lacosamide 200 and 400 mg/day, respectively ($P < 0.05$ vs. placebo for both doses), were observed compared with 21% for placebo. The proportion of patients showing at least a 50% reduction in seizure frequency was 26% in the placebo group, 35% in the 200 mg/day group, and 41% in the 400 mg/day group ($P < 0.01$ for the 400 mg/day group) [14,25].

In the third trial, 405 patients with refractory partial-onset seizures receiving up to three AEDs were randomized to placebo or to target lacosamide doses of 400 or 600 mg/day [26]. A reduction in seizure frequency of at least 50% was recorded in 38.3% of patients treated with 400 mg/day and in 41.2% of patients treated with 600 mg/day lacosamide compared with 18.3% of patients allocated to placebo. The difference versus placebo was statistically significant at both doses.

In conclusion, lacosamide demonstrated clear efficacy in a highly refractory population, with responder rates falling within the range of marketed AEDs [28]. Among the patients who completed the pivotal trials, 3.3% and 4.8% of those taking 400 mg/day and 600 mg/day lacosamide, respectively, were seizure free as compared with 0.9% of the patients in the placebo arm (Fig. 42.2). While these figures seem to be modest, the pivotal lacosamide trials were conducted in a highly refractory population [29].

Long-term efficacy in patients with partial-onset seizures

The long-term efficacy of lacosamide is being evaluated in open-label extension trials, which included patients who had participated in the double-blind studies. In an interim analysis of one of these trials, conducted 30 months after the last subject had entered the trial (exposure up to 5.5 years), the median modal dose was 400 mg/day. In general, the median percent reduction in seizure frequency across all treatment groups was 45.9%. In

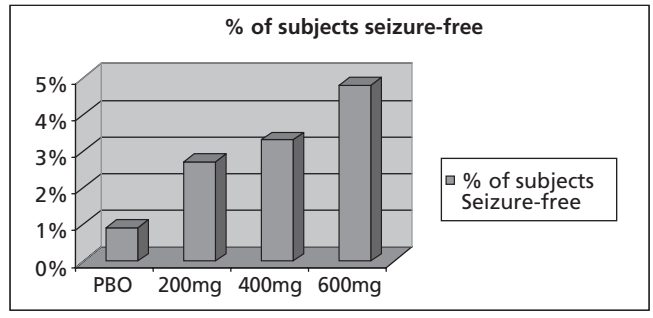

Fig. 42.2 Percentage of subjects who completed the trial and were seizure free during the double-blind maintenance phase in a pooled analysis of the three pivotal randomized placebo (PBO)-controlled adjunctive-therapy trials of lacosamide (200, 400 and 600 mg/day) in adults with refractory partial-onset seizures. From ref 29 with permission.

terms of responder rates, 46.6% of patients had a ≥50% reduction in seizures [30]. Some patients discontinued from the open-label trials due to lack of efficacy (as per protocol), which may have resulted in trends towards better efficacy over time. Therefore, these data should be viewed for descriptive purposes only.

Studies in non-epilepsy indications

A number of randomized placebo-controlled double-blind trials evaluated the potential value of lacosamide in patients with neuropathic pain secondary to distal diabetic neuropathy [31–34]. These studies suggest that lacosamide may be efficacious in attenuating pain in these patients at doses up to 400 mg/day. A dose of 600 mg/day did not appear to confer additional benefit and was less well tolerated.

Adverse effects

Most common adverse events reported in controlled trials

Adverse events observed during the lacosamide clinical programme seem to be consistent with its proposed mechanism of action. AEDs acting through the modulation of sodium currents are associated with dose-related central nervous system (CNS) and gastrointestinal system adverse effects. With lacosamide, dizziness, diplopia and headaches are the most commonly reported CNS adverse events, while nausea and vomiting are the most common gastrointestinal events; all of these events with the exception of headache were dose related (Table 42.2). Of importance, the incidence of somnolence [25] was relatively low, and very few patients treated with lacosamide complained of cognitive difficulties [35].

In the three pivotal, double-blind controlled trials, overall discontinuation rates during the treatment period were 18%, 23% and 38% in the groups assigned to lacosamide doses of 200 mg/day, 400 mg/day and 600 mg/day, compared with 13% among patients randomized to placebo [35]. Dizziness was the most common adverse event leading to premature withdrawal, especially in the 600 mg/day group.

Special safety issues

Lacosamide has been shown to have no effect on QTc interval in a definitive trial which tested doses of 800 mg/day in healthy volunteers [36].

A small, dose-related increase in PR interval was observed with lacosamide treatment. The mean increase from baseline to the end of the maintenance phase was 1.4 ms, 4.4 ms and 6.6 ms for 200, 400 and 600 mg/day lacosamide compared with a 0.3 ms decrease for placebo [34]. In epilepsy patients, the incidence rate of reported treatment-emergent first-degree atrioventricular (AV) block as an adverse event is uncommon (0.4% lacosamide and 0% placebo) [21]. Similar asymptomatic PR prolongations appear to be associated with other AEDs such as carbamazepine [37], lamotrigine [38] and pregabalin [39]. No second- or higher-degree AV block was seen in lacosamide-treated patients with epilepsy. The incidence of syncope was also low and did not differ between lacosamide-treated epilepsy patients (0.1%) and placebo-treated epilepsy patients (0.3%) [20].

In conclusion, the safety profile of lacosamide shows a predominance of dose-related nervous system and gastrointestinal adverse events. PR prolongation and first-degree AV block are being monitored in postmarketing safety studies.

As with all AEDs, suicidality and suicide should be closely monitored especially in the epilepsy population.

Table 42.2 Incidences of treatment emergent adverse events reported by ≥10% of subjects in any lacosamide treatment group, based on a pooled analysis of the three double-blind pivotal lacosamide trials in patients with refractory partial-onset seizures.

MedDRA system organ class preferred term	Placebo, % (*n* = 364)	Lacosamide 200 mg/day, % (*n* = 270)	Lacosamide 400 mg/day, % (*n* = 471)	Lacosamide 600 mg/day, % (*n* = 203)	Lacosamide total, % (*n* = 944)
Nervous system disorders					
Dizziness	8	16	30	53	31
Headache	9	11	14	12	13
Abnormal co-ordination	2	4	7	15	8
Tremor	4	4	6	12	7
Nystagmus	4	2	5	10	5
Eye disorders					
Diplopia	2	6	10	16	10
Vision blurred	2	2	8	16	8
Gastrointestinal disorders					
Nausea	4	7	11	17	11
Vomiting	3	6	9	16	9
General disorders and administration site conditions					
Fatigue	6	7	7	15	9

From ref. 35 with permission.

Place in current therapy

Lacosamide is a new chemical entity with a novel mode of action, i.e. enhanced slow inactivation of voltage-gated sodium channels and a potential interaction with CRMP-2; however, the precise interaction with CRMP-2 is not fully understood and, at this stage, its implications are rather speculative.

Lacosamide is approved as adjunctive therapy for the treatment of partial-onset seizures in subjects aged ≥16 years in Europe and in subjects ≥17 years in the USA. Lacosamide has a number of advantageous features, including predictable and linear pharmacokinetics with low intra- and inter-patient variability, a half-life compatible with twice-daily dosing, a low potential for drug–drug interactions, and consistent efficacy data when used as adjunctive therapy in adult patients with refractory partial epilepsy. Its potential usefulness in other epilepsy syndromes has not been investigated to date, and its role in the current treatment of epilepsy will be clarified when more extensive data from clinical studies and from postmarketing experience become available. Based on available data, the target dose range appears to be 200–400 mg/day, to be achieved with gradual titration. Although lacosamide 600 mg/day is not an approved dose by either the EMEA or FDA, some patients may benefit from treatment of up to 600 mg/day.

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43 Lamotrigine

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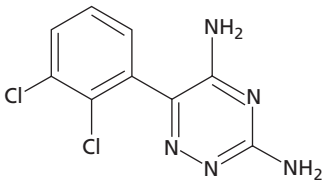

Primary indications	Adjunctive treatment and monotherapy of partial seizures (with or without secondary generalization) and primary generalized tonic–clonic seizures. Also useful for other generalized epilepsy syndromes, including Lennox–Gastaut syndrome, mostly as adjunctive therapy
Usual preparation	Regular tablets: 25, 50, 100, 150, 200 mg Dispersible tablets: 2, 5, 25, 100 mg Extended-release tablets: in development
Usual dosages	Lamotrigine should be titrated gradually according to pre-established guidelines up to the desired maintenance dose. The following maintenance dosages are often used: Combination therapy without valproic acid and without enzyme-inducing agents: 200–400 mg/day (children 2–12 years of age: 2.5–7.5 mg/kg/day) Initial monotherapy: 100–200 mg/day (over 12 years of age) Combination therapy with valproic acid without enzyme-inducing agents: 100–200 mg/day (children 2–12 years of age: 1–3 mg/kg/day) Combination therapy with enzyme-inducing agents without valproic acid: 300–500 mg/day (children 2–12 years of age: 5–15 mg/kg/day)
Dosing frequency	Once or twice daily, depending on expected half-life in the individual patient and type of formulation
Significant drug interactions	Serum lamotrigine levels are reduced by enzyme-inducing antiepileptic drugs, methsuximide, rifampicin, the lopinavir–ritonavir combination, combined steroid contraceptives and some other oestrogen-containing hormonal preparations. Serum lamotrigine levels are increased by valproic acid. Lamotrigine may reduce the serum levels of levonorgestrel
Serum level monitoring	Dosage is usually individualized based on clinical response. Serum drug level monitoring is particularly useful to guide dosage adjustments in situations associated with changes in lamotrigine pharmacokinetics, such as pregnancy, puerperium and drug–drug interactions
Reference range	2.5–15 mg/L
Common/important adverse effects	Dizziness, diplopia, ataxia, blurred vision, somnolence, insomnia, headache, nausea, asthenia, skin rash (including serious cutaneous reactions) and other hypersensitivity reactions
Main advantages	Relatively broad-spectrum efficacy against multiple seizure types and good tolerability, particularly when used as monotherapy
Main disadvantages	Need for slow-dose escalation. Highly variable pharmacokinetics in relation to physiological factors (e.g. pregnancy) and drug interactions

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Mechanism of action	Blockade of voltage-dependent sodium and calcium channels. Other mechanisms may contribute to antiepileptic efficacy
Oral bioavailability	>95%
Time to peak levels	1–3 h
Elimination	Primarily by conjugation with glucuronic acid
Volume of distribution	1.2 L/kg
Elimination of half-life	Patients on monotherapy, patients on polytherapy receiving neither valproic acid nor enzyme inducers, and patients receiving a combination of valproic acid and enzyme inducers: 25 h Patients receiving valproic acid without enzyme inducers: 60 h Patients receiving enzyme inducers without valproic acid: 13 h The above are mean values and intersubject variability is considerable. Children may have shorter half-lives
Serum clearance	Patients on monotherapy, patients on polytherapy receiving neither valproic acid nor enzyme inducers, and patients receiving a combination of valproic acid and enzyme inducers: 0.50 mL/min/kg Patients receiving valproic acid without enzyme inducers: 0.30 mL/min/kg Patients receiving enzyme inducers without valproic acid: 1.15 mL/min/kg The above are mean values and intersubject variability is considerable. Children have higher clearance values
Protein binding	55%
Active metabolites	None
Comment	A very useful antiepileptic drug which can used as first- or second-line monotherapy, or as adjunctive therapy, in the treatment of partial seizures and in some of the generalized epilepsy syndromes

Introduction

Lamotrigine was initially developed as a folate antagonist after the observation that patients with epilepsy treated with antiepileptic drugs (AEDs) had diminished levels of folic acid [1]. However, no correlation between antifolate effects and AED activity has ever been established, and lamotrigine's antiepileptic acitivity is considered to be mediated by actions other than its weak folate antagonistic properties.

Lamotrigine was introduced for the adjunctive treatment of partial seizures in the UK in 1991, in the USA in 1994, and later worldwide. Its use for initial monotherapy is approved in several countries, but not in the USA, where monotherapy can be attained by successful removal of concurrent AEDs. Its extensive use has also highlighted some unique issues. The manufacturer's product information is regularly updated, and the clinician should refer to the latest version (http://us.gsk.com/products/assets/us_lamictal.pdf).

Chemistry

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] has a molecular formula of $C_9H_7N_5Cl_2$, a molecular weight of 256.09 and pK_a of 5.7. It is a white to pale-cream-coloured powder, poorly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M hydrochloric acid (4.1 mg/mL at 25°C).

Pharmacology

Activity in animal models of seizures and epilepsy

A number of electrical, chemical and genetic models of seizures and epilepsy have indicated the therapeutic potential of lamotrigine in the treatment of partial, generalized tonic–clonic and absence seizures [2]. In seizure models, lamotrigine displays an antiepileptic profile broadly similar to that of phenytoin and carbamazepine [3,4]. Lamotrigine was more potent than phenytoin and carbamazepine in these models and in suppressing sound-induced clonic seizures in the genetically epilepsy-prone rat [5]. Compared with other newer AEDs, lamotrigine [intraperitoneal (i.p.) administration] was effective in antagonizing tonic convulsions in the maximal electroshock test, in which gabapentin, tiagabine and vigabatrin had no effect, and was ranked above these agents, in terms of therapeutic index, in the inhibition of sound-induced seizures in DBA/2 mice [6].

Lamotrigine differs from carbamazepine and phenytoin in its effects in some models of absence epilepsy. Even though in

the classic absence model (pentylenetetrazole-induced clonus) lamotrigine, like phenytoin and carbamazepine, failed to show any effect [4,6], in the lethargic mouse model of human absence seizures, i.p. lamotrigine was shown to reduce seizure frequency by 65% compared with vehicle, whereas vigabatrin and tiagabine significantly increased seizure frequency and gabapentin and topiramate had no effect [7].

Lamotrigine produces a dose-dependent suppression of secondary generalized seizures and afterdischarge duration in amygdaloid and hippocampal-kindled seizures in rats (a model of complex partial seizures), with the effect lasting as long as 24 h in some cases [6,8]. This effect was also observed in kindled rats which had previously showed no response to phenytoin. Lamotrigine is thought to produce this effect by increasing afterdischarge threshold, that is by suppression of seizure initiation, not propagation.

Activity in other experimental models

Lamotrigine confers protection against local cerebral ischaemia and reduces kainate-induced neurotoxicity in the rat, presumably by suppressing glutamate release [9–11]. In a rat model of neonatal hypoxic–ischaemic injury, i.p. administration of lamotrigine immediately post insult was shown to significantly decrease neuronal damage in the hippocampus with a concomitant decrease in the tissue levels of glutamate and aspartate and without altering the levels of γ-aminobutyric acid (GABA) [12].

Mechanism of action

Although structurally unrelated to phenytoin and carbamazepine, lamotrigine has been demonstrated to block sodium channels in a voltage-, use- and frequency-dependent manner, preventing propagation of action potentials [13–17] and the release of neurotransmitters, principally glutamate [18–21]. Lamotrigine inhibits voltage-sensitive sodium currents through a preferential interaction with the slow inactivated sodium channel [15], suggesting that it may act selectively against high-frequency epileptiform discharges [13]. In keeping with its cellular actions, lamotrigine suppresses burst firing in cultured rat cortical neurones and sustained repetitive firing in the mammalian spinal cord. Lamotrigine does not affect normal synaptic transmission in hippocampal slices, possibly due to preferential interaction with the slow inactivated sodium channel [22]. Lamotrigine potently inhibits glutamate and aspartate release induced by the sodium channel opener veratrine in rat cerebral cortical slices, and displaces batrachotoxin from its sodium channel-binding site [17,23]. Administration of a subconvulsive dose of *N*-methyl-D-aspartate (NMDA) antagonized the efficacy of lamotrigine in seizures induced by maximal electroshock by increasing its ED_{50} value, and this effect was reversed by simultaneous administration of NMDA receptor antagonists [24].

Lamotrigine has also been shown to modulate the calcium conductance involved in the release of excitatory amino acids in the corticostriatal pathway [21,25–27]. At clinically relevant concentrations, lamotrigine inhibits voltage-activated calcium currents in cortical and striatal neurones, an effect blocked by the N-type calcium channel blocker ω-conotoxin GVIA, but not by nifedipine (a dihydropyridine calcium receptor blocker). This action could inhibit glutamate release presynaptically, as well as prevent calcium overload in neurones through postsynaptic antagonism of voltage-dependent calcium channels [28].

Lamotrigine also appears to affect potassium conductance. In rat neocortical slices, lamotrigine was found to block epileptiform discharges induced by 4-aminopyridine, and in neocortical cell cultures, lamotrigine was shown to potentiate a 4-aminopyridine-sensitive hyperpolarizing potassium current [29].

Lamotrigine lacks any appreciable *in vitro* affinity for dopamine D_1 or D_2, α- or β-adrenergic, adenosine A1 or A2, muscarinic and σ-receptors, but has a weak inhibitory effect on serotonin 5-HT_3 receptors [13,30].

Current research on lamotrigine is also directed at assessing its effects on hippocampal neuronal networks potentially involved in its psychotropic action [31,32]. However, the full impact of data supporting inhibition of neurotransmitter release by lamotrigine should be further examined. Not readily understood is why lamotrigine has a much broader spectrum of clinical activity than either phenytoin or carbamazepine [33]. This difference cannot be easily reconciled by citing the lamotrigine-induced blockade of glutamate neurotransmitter release (an effect secondary to sodium channel blockade) because phenytoin and carbamazepine exhibit similar actions (again, under experimental conditions that may not be clinically relevant). The broader spectrum of activity of lamotrigine in different seizure types may be due to markedly preferential affinities for certain sodium channel subunit combinations, exhibiting differential regional distributions in the brain [34]. Alternatively, there may be an as yet unidentified mechanism of action for lamotrigine that might shed light on this difference.

Kynurenic acid is an endogenous excitatory amino acid receptor antagonist which acts as an antagonist at the glycine binding site on the NMDA receptor (see ref. 35 for review). It has shown antiseizure effect in various animal models. For example, kynurenic acid administration inhibited audiogenic seizures in DBA/2 mice [36]. Co-application of kynurenic acid into the hippocampus was shown to block seizure activity induced by quinolinic acid [37], and local injections of its analogue, 7-chlorokynurenic acid, were shown to delay the development of amygdala-kindled seizures [38]. Lamotrigine, along with other AEDs including phenobarbital, felbamate and phenytoin, was shown to enhance kynurenic acid production in rat cortical slices and to stimulate the activity of kynurenine aminotransferase-1 [39].

Pharmacokinetics

The pharmacokinetic profile of lamotrigine has been studied in the absence and in the presence of other AEDs after single [40–43] and multiple [44,45] doses in paediatric as well as adult patients. The pharmacokinetics of lamotrigine in adults has previously been extensively reviewed [46–49] (Table 43.1), but data in children are more complex (Table 43.2).

Lamotrigine pharmacokinetics is linear, and peak serum concentration (C_{max}) and area under the serum concentration–time curve (AUC) values are directly proportional to dose in the 30–450 mg range in both children and adults with epilepsy [48,50].

Absorption

Lamotrigine is well absorbed following oral administration, displaying an absolute bioavailability of 98% in healthy adult

Table 43.1 Mean[a] pharmacokinetic parameters of lamotrigine in healthy volunteers and in adult patients with epilepsy.

Adult study population	Number of subjects	Time of peak serum concentration (T_{max}) (h)	Half-life (h)	Apparent oral clearance (mL/min/kg)
Healthy volunteers taking no other medications				
Single-dose lamotrigine	179	2.2 (0.25–12.0)	32.8 (14.0–103.0)	0.44 (0.12–1.10)
Multiple-dose lamotrigine	36	1.7 (0.5–4.0)	25.4 (11.6–61.6)	0.58 (0.24–1.15)
Healthy volunteers taking valproic acid				
Single-dose lamotrigine	6	1.8 (1.0–4.0)	48.3 (31.5–88.6)	0.30 (0.14–0.42)
Multiple-dose lamotrigine	18	1.9 (0.5–3.5)	70.3 (41.9–113.5)	0.18 (0.12–0.33)
Patients with epilepsy taking valproic acid only				
Single-dose lamotrigine	4	4.8 (1.8–8.4)	58.8 (30.5–88.8)	0.28 (0.16–0.40)
Patients with epilepsy taking enzyme-inducing AEDs + valproic acid				
Single-dose lamotrigine	25	3.8 (1.0–10.0)	27.2 (11.2–51.6)	0.53 (0.27–1.04)
Patients with epilepsy taking enzyme-inducing AEDs[b]				
Single-dose lamotrigine	24	2.3 (0.5–5.0)	14.4 (6.4–30.4)	1.10 (0.51–2.22)
Multiple-dose lamotrigine	17	2.0 (0.75–5.93)	12.6 (7.5–23.1)	1.21 (0.66–1.82)

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[a] The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and apparent oral clearance and between 30% and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

[b] Examples of enzyme-inducing AEDs are carbamazepine, phenobarbital, phenytoin and primidone. Methsuximide, oestrogen-containing oral contraceptives, rifampicin and the lopinavir–ritonavir combination have also been shown to increase the clearance of lamotrigine.

Table 43.2 Mean pharmacokinetic parameters of lamotrigine in paediatric patients with epilepsy.

Paediatric study population	Number of subjects	Time to peak serum concentration (T_{max}) (h)	Half-life (h)	Apparent oral clearance (mL/min/kg)
Ages 10 months to 5.3 years				
Patients taking enzyme-inducing AEDs	10	3.0 (1.0–5.9)	7.7 (5.7–11.4)	3.62 (2.44–5.28)
Patients taking AEDs with no known effect on lamotrigine clearance	7	5.2 (2.9–6.1)	19.0 (12.9–27.1)	1.2 (0.75–2.42)
Patients taking valproic acid only	8	2.9 (1.0–6.0)	44.9 (29.5–52.5)	0.47 (0.23–0.77)
Ages 5–11 years				
Patients taking enzyme-inducing AEDs	7	1.6 (1.0–3.0)	7.0 (3.8–9.8)	2.54 (1.35–5.58)
Patients taking enzyme-inducing AEDs plus valproic acid	8	3.3 (1.0–6.4)	19.1 (7.0–31.2)	0.89 (0.39–1.93)
Patients taking valproic acid only[a]	3	4.5 (3.0–6.0)	65.8 (50.7–73.7)	0.24 (0.21–0.26)
Ages 13–18 years				
Patients taking enzyme-inducing AEDs	11			1.3
Patients taking enzyme-inducing AEDs plus valproic acid	8			0.5
Patients taking valproic acid only	4			0.3

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[a] Two subjects were included in the calculation for mean T_{max}.

volunteers. C_{max} occurs at approximately 1–3 h after oral administration in adults [46,48,51], and 1–6 h in children [40,43]. A second peak or plateau may occur at 4–6 h post dose, which is possibly due to enterohepatic recycling of the drug [50]. C_{max} was 1.6 mg/L after a single oral dose of 120 mg in adults, while after a single oral dose of 2 mg/kg a mean C_{max} of 1.48 mg/L was attained in 12 children aged between 6 months and 12 years. Lamotrigine absorption is not appreciably altered by the presence of food.

An extended-release formulation currently in development is associated with a smoother absorption profile, with peak concentrations occurring 4–11 h post dose and reduced fluctuations in serum drug levels during a dosing interval [52].

Distribution

Lamotrigine is approximately 55% bound to plasma proteins *in vitro*. Protein binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital and valproic acid [48].

The volume of distribution was 1.2 L/kg in healthy adult volunteers (range 0.87–1.3 L/kg) [46] and 1.5 L/kg in 12 children with epilepsy receiving single doses of lamotrigine (2 mg/kg) in the absence of other AEDs [40].

Studies in animals show that lamotrigine is widely distributed in all tissues and organs, but little is known of its differential tissue distribution in humans. In 11 adults undergoing neurosurgical intervention, lamotrigine showed good penetration into the brain, with a brain–serum lamotrigine concentration ratio of 2.8 [53,54]. Studies of cerebrospinal fluid (CSF) in children and young adults showed a CSF–serum concentration ratio of 0.43 [41].

Elimination

Lamotrigine is extensively metabolized by the liver, predominantly via N-glucuronidation, which is the rate-limiting step in lamotrigine elimination [46]. Approximately 70% of a single oral dose is recovered in the urine during the first 6 days, of which 80–90% is in the form of the 2-N-glucuronide metabolite, and the remainder in the form of the 5-N-glucuronide and parent drug. About 2% of an oral dose is excreted in the faeces.

The apparent oral clearance of lamotrigine shows great interindividual variation and is significantly influenced by concomitant medication and age [55]. Clearance is increased by 20–170% in children, but not for the first week of life. In comparative studies of lamotrigine monotherapy, apparent oral clearance and volume of distribution values were higher in children (0.038 L/h/kg and 1.5 L/kg) [40] than in adults (0.021–0.035 L/h/kg and 0.9–1.3 L/kg respectively), whereas elimination half-lives were broadly similar in children and in adults (32.3 h in children versus 23–37 h in adults). In the study in children, weight-normalized clearance appeared to be higher in children younger than 6 years (0.05 L/h/kg) than in children aged 6–11 years (0.033 L/h/kg) [40]. Age-related differences in lamotrigine clearance could be attributed to a relative reduction in liver size and hepatic blood flow in adolescents compared with young children [44,56].

In adults, the pharmacokinetics of lamotrigine after multiple dose administration conforms to that predicted from single-dose studies [46], indicating that clinically significant autoinduction does not occur [57]. In keeping with this, lamotrigine does not induce hepatic cytochrome P450 (CYP) enzyme activity after repeated administration [58].

Diminished glucuronidation of lamotrigine accounts for an age-related decline in the clearance of the drug in the elderly [55]. A comparison of the pharmacokinetics of lamotrigine (150-mg oral dose) in healthy young (26–38 years) and elderly (65–76 years) volunteers revealed a 37% lower serum clearance in the elderly, associated with 27% higher C_{max} and 55% higher AUC values [59].

Factors (other than age and co-medication) that affect lamotrigine pharmacokinetics

Pregnancy and lactation

The clearance of lamotrigine increases progressively until 32 weeks of gestation [60,61], a change which is associated with a corresponding lowering of serum lamotrigine concentration [62]. These changes are rapidly reversible after delivery, resulting in a prominent increase in serum lamotrigine concentration during the first few days post partum. The alteration in lamotrigine kinetics during pregnancy is often associated with increased seizure recurrence rates [62,63], and may require lamotrigine dose adjustment. The changes in lamotrigine pharmacokinetics during pregnancy seem to be much less significant in women treated with a combination of lamotrigine and valproic acid [64].

Lamotrigine is excreted in considerable amounts in breast milk, which in combination with slow elimination of the drug in the infants may result in lamotrigine serum concentrations in nursed infants comparable to those observed in patients receiving therapeutic doses [65]. A group of nine mothers (10 infants) were investigated as they delivered and breastfed their infants for 2–3 weeks [66]. At delivery, maternal lamotrigine serum concentrations were similar to those found in cord blood, indicating extensive placental transfer [67]. There was a slow decline in serum concentration in the newborn and, at 72 h post partum, median serum lamotrigine concentrations in the infants were 75% of the cord serum concentration (range 50–100%). The median milk–maternal serum concentration ratio was 0.61 (range 0.47–0.77) 2–3 weeks after delivery, and the nursed infant maintained serum lamotrigine concentrations of approximately 30% of the mother's serum concentration. A similar relationship between serum concentration in nursed infants and maternal lamotrigine concentration was reported at day 10 post partum in another study [68]. Maternal serum concentrations increased during the first 2 weeks post partum, the median increase in serum concentration–dose ratio being 170%. No adverse effects have been reported in the infants.

Gilbert's syndrome

Gilbert's syndrome, a disorder of conjugation characterized by disturbances in bilirubin metabolism and uridine diphosphate glucuronyl transferase (UGT) activity, is associated with a reduced rate of lamotrigine clearance and with prolongation by approximately 35% of lamotrigine half-life. In general, however, lamotrigine half-lives in subjects with Gilbert's syndrome remain within the range reported for healthy subjects [59].

Renal insufficiency

Twelve volunteers with chronic renal failure (mean creatinine clearance 13 mL/min; range 6–23 mL/min) and another six individuals undergoing haemodialysis were each given a single 100-mg dose of lamotrigine [69]. The mean lamotrigine half-lives determined in the study were 42.9 h (chronic renal failure), 13.0 h (during haemodialysis) and 57.4 h (between haemodialysis), compared with 26.2 h in healthy volunteers. On average, approximately 20% (range 5.6–35.1%) of the amount of lamotrigine present in the body was eliminated by haemodialysis during a 4-h session.

Hepatic disease

The pharmacokinetics of lamotrigine following a single 100-mg dose was evaluated in 24 subjects with mild, moderate and severe hepatic dysfunction (Child–Pugh classification system) and compared with that of 12 subjects without hepatic impairment [69]. The patients with severe hepatic impairment were without ascites ($n = 2$) or with ascites ($n = 5$). The mean apparent oral clearance

of lamotrigine in patients with mild (n = 12), moderate (n = 5) and severe liver impairment without ascites (n = 2) and severe liver impairment with ascites (n = 5) was 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04 and 0.15 ± 0.09 mL/min/kg, respectively, compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. The mean half-life of lamotrigine in patients with mild, moderate and severe liver impairment without ascites, and severe liver impairment with ascites was 46 ± 20, 72 ± 44, 67 ± 11 and 100 ± 48 h, respectively, compared with 33 ± 7 h in healthy subjects.

Drug interactions

Lamotrigine is most often used in combination with other AEDs, so a clear understanding of possible interactions between lamotrigine and co-administered drugs is important [70–72]. Although lamotrigine has little influence on the pharmacokinetics of other AEDs, the pharmacokinetics of lamotrigine can be markedly influenced by concomitant medications. Pharmacodynamic interactions between lamotrigine and other AEDs also occur.

Effects of co-administered drugs on lamotrigine pharmacokinetics

Other antiepileptic drugs

Co-administration of valproic acid, an inhibitor of glucuronidation, markedly reduces the rate of lamotrigine elimination (Tables 43.1 and 43.2) [73]. As shown in studies in children and adults, the half-life of lamotrigine is approximately doubled (to approximately 45–65 h) in patients receiving concomitant valproic acid compared with values in subjects receiving lamotrigine monotherapy. A study with healthy volunteers employed a single lamotrigine dose of 25 mg and evaluated the alterations of lamotrigine pharmacokinetics at valproic acid doses of 125, 250, 375 and 500 mg/day [74]. A change in the half-life of lamotrigine was demonstrable at a valproic acid dose of 125 mg/day. Maximal inhibition of lamotrigine metabolism is generally achieved at a valproic acid dose of about 500 mg/day. This pharmacokinetic interaction is thought to explain the increased incidence of rash seen after starting add-on lamotrigine in patients receiving valproic acid therapy.

Co-administration of drugs that induce the hepatic drug-metabolizing enzymes, such as phenytoin, carbamazepine and phenobarbital, increases the rate of elimination of lamotrigine, more than halving its half-life (to approximately 7–14 h) in some clinical trials compared with lamotrigine alone. Phenytoin appears to have a slightly greater effect on serum lamotrigine concentrations (decreases steady-state serum lamotrigine concentration by 45–54%) than carbamazepine, phenobarbital or primidone (decreases of approximately 40%). The effect of enzyme-inducing AEDs on lamotrigine appears to be more pronounced in children than in adults. This increased clearance, especially in children aged under 6 years, is likely to result in pronounced peak–trough fluctuations in serum lamotrigine concentrations at steady state [48]. Lamotrigine de-induction was studied by stepwise withdrawal (weekly 20% decrement) of carbamazepine or phenytoin as a part of an active control study [75]. Phenytoin withdrawal was followed by a 160% increase in serum lamotrigine concentration (n = 28), while carbamazepine withdrawal (n = 48) was associated with a 60% increase. Methsuximide has also been reported to decrease markedly serum lamotrigine levels [76].

Lamotrigine half-life is about 4- to 10-fold higher in patients given concomitant valproic acid than in those receiving enzyme-inducing AEDs (Tables 43.1 and 43.2), and steady-state dose-normalized serum lamotrigine concentrations are also increased or decreased accordingly [44,65]. Conversely, patients co-medicated with both valproic acid and enzyme-inducing AEDs have lamotrigine half-lives comparable to those described in subjects on lamotrigine monotherapy.

Because of the interactions described above, lamotrigine dosage must be adjusted according to the type of concomitant medication used. A recent population pharmacokinetic model for children has confirmed the effects of other AEDs on lamotrigine clearance and has been used to develop dose escalation schedules for concomitant therapy [56]. The new guidelines include lower initiation doses and a slower escalation rate, designed to generate average serum concentrations in children close to and not higher than those in adults under the current dosage guidelines [77].

Apart from valproic acid and enzyme-inducing AEDs, other AEDs are not expected to influence lamotrigine pharmacokinetics [71,78]. While some reports have suggested that lamotrigine clearance may be accelerated by oxcarbazepine, a carefully conducted study in healthy volunteers found no evidence of a pharmacokinetic interaction between these drugs [79].

Oral contraceptives and hormone replacement therapy

Addition of combined contraceptive steroids to the therapeutic regimen of women stabilized on lamotrigine results in a prominent drop in serum lamotrigine concentrations, to an average of about one-half the pre-interaction level [80]. The interaction, which appears to be due to stimulation of lamotrigine metabolism by the oestrogen component of the contraceptive, may result in loss of seizure control if lamotrgine dosage is not appropriately adjusted. Conversely, cessation of intake of the contraceptive results in a marked rise in serum lamotrigine levels, with the attendant risk of manifestations of toxicity. It has also been shown that in women stabilized on an oral contraceptive, the interaction follows a cyclic pattern, with a fall in serum lamotrigine levels during the (usually) 21-day period of intake of the contraceptive pill, and a transient increase in lamotrigine levels during the 7-day pill-free interval [80,81]. Interestingly, concomitant intake of valproic acid seems to antagonize the stimulating effects of steroid contraceptives on lamotrigine metabolism, and in women co-medicated with valproic acid serum lamotrigine levels appear to be comparable in the presence and in the absence of contraceptive pill use [64].

Hormone replacement therapy in postmenopausal women also seems to have significant effects on lamotrigine pharmacokinetics. In a randomized placebo controlled trial of hormone replacement therapy in women with epilepsy, two lamotrigine-treated women had a decrease in serum lamotrigine levels of 25–30% following administration of conjugated equine oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg, and in one of these women this was associated with worsening in seizure frequency [82].

Other drugs

Rifampicin and a combination of lopinavir or ritonavir have been found to affect lamotrigine clearance similarly to enzyme-inducing AEDs. Olanzapine causes a modest (about 25%) reduction in serum lamotrigine levels [83]. A slight reduction in serum lamotrigine levels was also noted with co-administration of paracetamol (acetaminophen), 900 mg three times daily, but this effect is unlikely to be of clinical importance [84]. There is anecdotal evidence that sertraline may increase serum lamotrigine levels. Clinical experiences from an expanding range of co-administered medications, including psychoactive drugs [85], are available (Table 43.3).

Table 43.3 Summary of drug interactions with lamotrigine.

Drug	Serum drug concentration with adjunctive lamotrigine[a]	Serum lamotrigine concentration with adjunctive drug[b]
Bupropion	n/a	⇌
Carbamazepine	⇌	–
Carbamazepine-10,11-epoxide[e]	?	n/a
Felbamate	n/a	⇌
Gabapentin	n/a	⇌
Hormone replacement therapy (e.g. equine oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg)[c]	n/a	–
Levetiracetam	⇌	⇌
Lithium	⇌	n/a
Lopinavir–ritonavir combination	⇌	–
Methsuximide	n/a	–
Olanzapine	⇌	⇌[f]
Oral contraceptives (e.g. ethinylestradiol/levonorgestrel)[c]	⇌[d]	–
Oxcarbazepine	⇌	⇌
Oxcarbazepine monohydroxy metabolite[g]	⇌	n/a
Paracetamol	⇌	⇌[f]
Phenobarbital/primidone	⇌	–
Phenytoin	⇌	–
Pregabalin	⇌	⇌
Rifampicin	n/a	–
Topiramate	⇌[h]	⇌
Valproic acid	–	+
Valproic acid + phenytoin and/or carbamazepine	n/a	⇌
Zonisamide	n/a	⇌

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⇌, neutral; –, decrease; +, increase; n/a: not assessed; ?, conflicting data.

[a] From adjunctive clinical trials and volunteer studies.

[b] Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.

[c] The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials and the effect may not be similar to that seen with the hormonal products tested.

[d] Modest decrease in levonorgestrel.

[e] Not administered, but an active metabolite of carbamazepine.

[f] Slight decrease, not expected to be clinically relevant.

[g] Not administered, but an active metabolite of oxcarbazepine.

[h] Slight increase not expected to be clinically relevant.

Effects of lamotrigine on the pharmacokinetics of co-administered drugs

Other AEDs

In contrast to many other AEDs, lamotrigine does not appear to inhibit or induce the hepatic CYP drug-metabolizing enzymes [58] or displace other AEDs from serum proteins [46]. Therefore, the pharmacokinetic profiles of most conventional AEDs are not significantly altered when lamotrigine is added or withdrawn [40,86–88] (Table 43.3). In at least one study, however, the addition of lamotrigine to steady-state valproic acid treatment in adult volunteers resulted in a 25% reduction in serum valproic acid concentrations [89].

Oral contraceptives

In a carefully conducted study designed to assess the interaction between lamotrigine and steroid oral contraceptives, lamotrigine (titrated up to 300 mg/day) did not affect the pharmacokinetics of ethinylestradiol in 16 evaluable healthy female volunteers but decreased levonorgestrel moderately, by an average of 19% [80]. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations were increased by 4.7-fold and 3.4-fold respectively in the presence of lamotrigine, but serum progesterone concentrations were low, suggesting that suppression of ovulation was maintained. Intermenstrual bleeding was reported by 32% of women during co-administration of lamotrigine and a combined oral contraceptive.

Pharmacodynamic interactions

In addition to pharmacokinetic interactions, pharmacodynamic interactions between lamotrigine and other AEDs have been reported.

Synergistic therapeutic effects, as well as some adverse effects (particularly development of tremor), have been observed [45,90] when combining lamotrigine and valproic acid, an interaction that cannot always be explained by the elevating effect of valproic acid on serum lamotrigine concentration.

On the other hand, an adverse pharmacodynamic interaction between lamotrigine and carbamazepine has been observed. Diplopia, dizziness, nausea, ataxia and nystagmus – classic signs of carbamazepine toxicity – were reported in some adult and child patients when lamotrigine was added to carbamazepine therapy [91,92]. This was originally thought to be attributable to increases in the serum concentrations of the active metabolite carbamazepine-10,11-epoxide. However, the effects of lamotrigine on the serum concentration of carbamazepine-10,11-epoxide are ambiguous. In adults, the addition of lamotrigine to existing carbamazepine therapy has variously been reported to increase serum carbamazepine-10,11-epoxide concentrations by 10–45% [92] or to leave them unaltered [93,94]. In children, the mean serum concentration of carbamazepine-10,11-epoxide decreased significantly when lamotrigine was added to carbamazepine therapy in one study [95]. A pharmacodynamic interaction resulting in reciprocal facilitation of adverse effects has also been reported between lamotrigine and oxcarbazepine [79].

Serum level monitoring

A clear relationship between serum lamotrigine concentrations and clinical response has not been established in clinical trials [96]. A target range of between 1 and 4 mg/L was initially suggested [86,97,98] but children and adults with refractory epilepsy frequently require higher serum concentrations to gain optimum seizure control [99,100]. Although dose-related improvements in seizure control have been observed in children over the serum concentration range of 4–21 mg/L [99], most investigators have not found this [45,78,101]. More recent recommendations for a reference range are 1–13 mg/L [102], 3–14 mg/L [103] and 2.5–15 mg/L [104].

Likewise, there is a variable relationship between serum concentration and incidence of adverse events [45,101,105,106], although some studies do suggest that a useful correlation does exist. In a paediatric study of high-dose lamotrigine therapy, increases in lamotrigine serum concentrations above 21 mg/L were prevented because of the development of unacceptable levels of nausea that did not resolve with reduction of concomitant medications [99]. In a retrospective study of 811 patients, reviewing 3731 lamotrigine serum concentrations [107], the proportion of patients with manifestations of toxicity was 7% at concentrations <5.0 mg/L, 14% at concentrations of 5–10 mg/L, 24% at concentrations from 10 to 15 mg/L, 34% at concentrations from 15 to 20 mg/L and 59% at concentrations >20 mg/L. The correlation between serum lamotrigine levels and tolerability was independent of concurrent medication.

Although lamotrigine dosage is usually individualized on the basis of clinical response, serum drug level monitoring is very useful to guide dosage adjustments in situations associated with changes in lamotrigine pharmacokinetics, such as pregnancy, puerperium and drug–drug interactions.

Efficacy

Pivotal randomized clinical trials of the antiepileptic efficacy of lamotrigine involved adults with refractory partial epilepsies. More recent clinical trials have evaluated lamotrigine in generalized epilepsies, in children, in the elderly, and in monotherapy and long-term use.

Adjunctive therapy studies in refractory partial epilepsy

A large number of short-term randomized double-blind placebo-controlled studies, many with a cross-over design, have confirmed the efficacy of lamotrigine when used as add-on therapy in patients with refractory partial epilepsy [86–88,98,108–116] (Table 43.4). One of the studies has been published in abstract form only [116]. The results of a meta-analysis, incorporating some unpublished data, are also available [117].

In these studies, addition of lamotrigine 50–500 mg/day resulted in a 13–59% reduction in total seizure frequency, with responder rates (proportion of patients experiencing greater than 50% seizure reduction) ranging from 7% to 67%. In the largest of the studies, a multicentre parallel-group trial of 24 weeks' duration [112], lamotrigine 500 mg/day proved to be more effective than lamotrigine 300 mg/day or placebo as add-on therapy, reducing total seizure frequency by 36%, with a responder rate of 34%.

In a large double-blind paediatric multicentre study in the USA [110], a total of 199 patients were randomized to lamotrigine (n = 98) and placebo (n = 101). Over the entire study duration of 18 weeks, a greater than 50% reduction in partial seizures compared with baseline was seen in 42% in lamotrigine-treated patients and 16% of placebo-treated patients.

The most recent double-blind parallel-group study, which allowed a wider range of concomitant AEDs including carbam-

Table 43.4 Double-blind, placebo-controlled efficacy trials of lamotrigine as add-on therapy in partial epilepsy.

Reference	Number of patients randomized	Baseline seizure frequency (seizures/month)	Dosage in mg/day (number of patients per group)	Median reduction in seizure frequency in the lamotrigine group (%)	Patients with at least 50% seizure reduction in the lamotrigine group (%)
Binnie *et al*. [109][a]	30	≥4	75–200 (30)	17	7
Jawad *et al*. [86][a]	21	16	75–400 (21)	59	67
Loiseau *et al*. [87][a]	23	≥4	75–300 (23)	23	30
Matsuo *et al*. [112]	191	≥4	300 (65) 500 (59)	20 (placebo 8) 36 (placebo 8)	20 (placebo 18) 34 (placebo 18)
Messenheimer *et al*. [113][a]	88	≥3	100–400 (88)	25	20
Sander *et al*. [88][a]	18	≥4	100–300 (18)	18	
Schapel *et al*. [115][a]	41	17 (median)	150–400 (41)	24	22
Schmidt *et al*. [116][a]	21		Up to 300 (21)	21.9	29
Smith *et al*. [108][a]	62		100–400 (62)	30	18
Stolarek *et al*. [98][a]	20	≥3	50–200 (20)	37	45
Boas *et al*. [110][a]	56	≥4	100–400 (56)	30	24
Duchowny *et al*. [111]	199	≥4	Age–weight adjusted	36.1 (placeb: 6.7)	42 (placebo 16)
Naritoku *et al*. [114]	116	≥4	200 mg (valproic acid) 500 mg (enzyme-inducing AEDs)[b] 300 mg (non-enzyme-inducing AEDs)[c]	46 (placebo 24)	42 (placebo 24)

[a] Cross-over design.

[b] Carbamazepine, phenobarbital, phenytoin.

[c] Topiramate, oxcarbazepine, levetiracetam.

azepine, valproic acid, topiramate, oxcarbazepine, phenytoin and levetiracetam (in a decreasing number of patients), employed an extended-release formulation of lamotrigine at three different dosing schedules according to the type of concomitant AEDs: valproic acid, enzyme-inducing AEDs and non-enzyme-inducing AEDs [114]. The patients were 12 years or older, and those implanted with a vagus nerve stimulator were also eligible. Over the entire study of 19 weeks, the median reduction in seizure frequency in the lamotrigine group was 46% (compared with 24% for the placebo group) and a greater than 50% seizure reduction was seen in 42% of patients (compared with 24% for the placebo group).

Conversion to monotherapy studies in refractory epilepsy

A double-blind, short-term active-control study in adolescent and adult patients with refractory partial epilepsy further confirmed the efficacy of lamotrigine in partial epilepsy [118]. A total of 156 patients on monotherapy with carbamazepine or phenytoin were assigned to lamotrigine or valproic acid. While maintaining the concomitant drug at a steady dose level during baseline, the lamotrigine group underwent a dose escalation to the target dose of 500 mg daily while the valproic acid group was escalated to 1000 mg daily, a minimally effective dose. Concomitant medication was gradually tapered, and patients exited the study if seizure deterioration occurred. Overall, 50 and 64 subjects in the lamotrigine and in the valproic acid group, respectively, achieved monotherapy. The lamotrigine group, however, was more successful in completing the 12-week monotherapy phase (56% versus 20%), and the median time to meet escape criteria for seizure deterioration was significantly shorter for the valproic acid group (57 days versus 168 days).

In a complex non-randomized multicentre study, four groups of patients on monotherapy with valproic acid (n = 117), carbamazepine (n = 129), phenytoin (n = 92) and phenobarbital (n = 9) were recruited, and lamotrigine was added to the concomitant AED to the target daily dose of 100 mg for the valproic acid group and 400 mg for the other groups [119]. The concomitant AED was then withdrawn and lamotrigine monotherapy was attained. Lamotrigine dose was adjusted in the valproic acid group as valproic acid was withdrawn. In the remaining groups, serum lamotrigine concentration rose as the concomitant drug was withdrawn. A greater than 50% seizure reduction during the add-on phase was seen in 47% (64% with valproic acid; 41% with carbamazepine; 38% with phenytoin), and the responder rate was higher in patients with 'idiopathic' tonic–clonic seizures (61%) than in those with partial seizures (43%). There were more responders in the valproic acid group, but statistical significance was reached for the partial seizures group only. Although the valproic acid group experienced better seizure control during the add-on phase than the other groups, more patients in the valproic acid group tended to deteriorate during the phase of conversion to lamotrigine monotherapy. These results were interpreted as evidence of synergism between lamotrigine and valproic acid.

A multicentre study from Poland recruited two equal groups of 63 patients with uncontrolled seizures on monotherapy with carbamazepine or valproic acid [120]. The four study phases consisted of (1) 4-week lamotrigine dose escalation; (2) 8-week lamotrigine add-on therapy; (3) 8-week carbamazepine/valproic acid withdrawal if clinically appropriate; and (4) 8-week lamotrigine monotherapy. Of 126 patients, 107 (85%) completed dose escalation and add-on therapy, and 85 (68%) completed the lamotrigine monotherapy phase. A greater than 50% seizure reduction occurred in 50% of patients during add-on therapy and in 53% during lamotrigine monotherapy, and 27% were seizure free during lamotrigine monotherapy. Fakhoury *et al.* [121] reported the US multicentre data from a similar large international open-label conversion to monotherapy study, consisting of two arms (lamotrigine versus carbamazepine and lamotrigine versus valproic acid) in the same four phases. The 144 patients in the carbamazepine arm were randomly assigned to add-on lamotrigine (98 patients) and add-on carbamazepine (46 patients) before withdrawing concomitant medication. Monotherapy was completed (at least 7 weeks) in 56% of lamotrigine patients and 54% of carbamazepine patients. Seizure freedom was attained during the monotherapy phase in 41% of lamotrigine patients and 30% of carbamazepine patients. Neither of these differences was significant. Among the 158 patients in the valproic acid arm (105 assigned to lamotrigine and 53 to valproic acid), monotherapy was completed in 49% of lamotrigine patients and 40% of valproic acid patients. Statistical significance was attained in seizure freedom during the monotherapy phase with 32% versus 11% in favour of lamotrigine.

Monotherapy studies in newly diagnosed (predominantly partial) epilepsy

As monotherapy, lamotrigine is as effective as carbamazepine, phenytoin and gabapentin against partial-onset seizures and secondary generalized tonic–clonic seizures (Table 43.5). Four studies [122–125] enrolled children, while nine [122–130] were conducted in adults, including four trials in the elderly [126–129].

Five randomized trials comparing lamotrigine and carbamazepine required multiple seizures for entry [122,123,126,129,131], and three required a minimum of only one seizure [124,127,128]. One study [122] was exceptional, because eligibility criteria also allowed inclusion of 233 patients between 2 and 12 years of age, and was limited to partial epilepsy. Three studies [126,128,129] recruited elderly patients only (with the oldest being 91 years of age), and other studies included adolescent patients as well. Lamotrigine and carbamazepine were similar in efficacy, when evaluated in a diverse range of patient populations. They differed, however, in tolerability, because withdrawal secondary to treatment-emergent adverse events was more likely with carbamazepine, possibly most significantly in children and the elderly [122,126,128,129]. In the studies for which only one seizure was required for entry [124,127,128], seizure freedom attained tended to be higher for both agents, without statistically significant differences.

In one randomized comparative trial, lamotrigine and phenytoin were similarly effective [132] in terms of time to the first seizure and time to discontinuation. The recruited patients ranged from 14 to 75 years of age, and patients with primary generalized tonic–clonic seizures were eligible. Adverse events led to discontinuation of 13 patients (15%) in the lamotrigine group and 18 (19%) in the phenytoin group.

Table 43.5 Comparative trials of lamotrigine in newly diagnosed patients with epilepsy.

Reference	Number of patients on entry	Dosage (mg/day)	Study duration	Proportion of patients seizure free during final 24 weeks of treatment (%)	Proportion of patients completing study (%)
Versus carbamazepine					
Brodie *et al*. [131]	131	Lamotrigine 100–300 (median 150)	48	39	65
	129	Carbamazepine 300–1400 (median 600)		38	51
Reunamen *et al*. [123]	115	Lamotrigine 100	30	51	62
	111	Lamotrigine 200		60	69
	117	Carbamazepine 600		55	65
Brodie *et al*. [126] (elderly trial)	102	Lamotrigine 75–300 (median 100)	24	38[a]	71
	48	Carbamazepine 200–800 (median 400)		44[a]	42
Nieto-Barrera *et al*. [122] (partly paediatric trial)	417	Lamotrigine 50–300 (median 100)	24	65[b]	81
	201	Carbamazepine 100–1500 (median 400)		73[b]	77
Rowan *et al*. [128][c] (elderly trial)	200	Lamotrigine 150	52	51	56
	198	Carbamazepine 600		64	35
Saetre *et al*. [129] (elderly trial)	93	Lamotrigine 25–400 (median 100)	40	57	68
	91	Carbamazepine sustained-release 100–800 (median 400)		52	61
Steinhoff *et al*. [124][c]	88	Lamotrigine 75–300 (median 200)	24	89[d]	91
	88	Carbamazepine 450–1800 (median 900)		94[d]	81
Gilad *et al*. [127][c]	32	Lamotrigine		72	87
	32	Carbamazepine		44	69
Versus phenytoin					
Steiner *et al*. [132]	86	Lamotrigine 100 or more (mode 150)	48	43	48
	95	Phenytoin 200 or more (mode 300)		36	47
Versus gabapentin					
Brodie *et al*. [130]	143	Lamotrigine 150	24	76	67
	148	Gabapentin 1800		76	72
Rowan *et al*. [128][c] (elderly trial)	200	Lamotrigine 150	52	51	56
	195	Gabapentin 1500		47	49
Versus valproic acid					
Stephen *et al*. [125]	114	Lamotrigine 150–600 (median 200)	104	47	62
	111	Valproic acid 600–3000 (median 1000)		47	50
Steinhoff *et al*. [124][c]	33	Lamotrigine 75–300 (median 150)	24	61[d]	88
	30	Valproic acid 600–2100 (1050 median)		84[d]	97

[a] Data were collected for 16 weeks.
[b] For patients older than 13 years only.
[c] At least one seizure before entry.
[d] Data were derived from the final 8 weeks. Marked seizure freedom difference in the trial versus valproic acid (not statistically significant) was attributed to worse outcome in 10 lamotrigine patients with juvenile myoclonic epilepsy.

Lamotrigine and gabapentin were similar in efficacy in two randomized studies [128,130]. One study recruited the elderly (60 years of age or older) and most of the patients had symptomatic epilepsy [128]. The other included patients 16 years or older (with one exceptional patient at 13 years of age, and the oldest at 78), and patients with primary generalized tonic–clonic seizures were eligible [130].

Lamotrigine was compared with valproic acid in two studies of newly diagnosed patients. One study with 225 patients (aged between 13 and 80 years) consisted of 161 patients with partial epilepsies, 47 with generalized tonic–clonic seizures and 17 with juvenile myclonic epilepsy [125]. Seizure freedom was attained in 47% of patients for both lamotrigine and valproic acid, while more patients withdrew from valproic acid secondary to adverse events, including eight patients with excessive weight gain. In the other study, which required only one seizure (partial or generalized) for entry [124], 63 out of 239 patients (with 33 patients younger than 18) had generalized epilepsies and neither seizure freedom nor withdrawal rates were statistically different between groups However, seizure freedom was more often associated with valproic acid in patients with juvenile myclonic epilepsy – 3 out of 10 in the lamotrigine group versus 3 out of 4 in the valproic acid group.

A randomized parallel-group comparison of lamotrigine with several other AEDs in patients with newly diagnosed epilepsy was conducted recently within the context of the SANAD collaboration [133,134]. This was a UK government-sponsored long-term study of AED efficacy and tolerability, comparing newer AEDs with two recognized first-line AEDs, carbamazepine (arm A, including mostly patients with partial epilepsies) and valproic acid (arm B, including mostly generalized and unclassifiable epilepsies). Neither the prescribing physician nor the patient was blinded, and patients were randomly assigned one of four AEDs, carbamazepine, lamotrigine, gabapentin or topiramate, for arm A ($n = 1721$), and one of three AEDs, valproic acid, lamotrigine or topiramate, for arm B ($n = 716$). Enrolment began in 1999, and data collection was completed in 2006. The study added oxcarbazepine to arm A in 2001 but levetiracetam and zonisamide were not included. AED dosing guidelines were provided, but the prescribing physician controlled AED dosing in order to maximize the benefit of the assigned AED. The primary outcomes were time to treatment failure and time to 12-month remission. The secondary outcomes were time from randomization to a first seizure, time to 2-year remission, the incidence of clinically important adverse events and adverse effects emerging after randomization. For arm A (partial epilepsies), lamotrigine was significantly better than carbamazepine, gabapentin and topiramate for time to treatment failure, but its advantage over oxcarbazepine was not significant [133]. Carbamazepine had a non-significant advantage over lamotrigine, topiramate and oxcarbazepine for time to 12-month remission. A per-protocol analysis supported non-inferiority of lamotrigine compared with carbamazepine. The results for arm B of the study are reported below in the section 'Monotherapy studies in newly diagnosed generalized and unclassifiable epilepsies'.

Adjunctive therapy studies in generalized epilepsy

In a multicentre double-blind cross-over study, a total of 26 patients with various generalized epilepsies, including absence, were randomized to lamotrigine (at a maintenance dose of either 75 or 150 mg daily, depending on the concomitant AED) or placebo, added on to the existing regimen [135]. Twenty-two patients completed the placebo-controlled phase. A greater than 50% seizure reduction occurred in 50% of patients with tonic–clonic seizures, and in 33% of those with absence seizures. In the continuation phase, five patients (25%) remained seizure free.

In a single-centre study employing an innovative design [136], 17 patients (57%) experienced a greater than 50% seizure reduction when lamotrigine was added on in an initial open-label phase. Fifteen of the responders were then assigned, according to a double-blind cross-over design, to lamotrigine or placebo after a washout period, with the two double-blind phases consisting of 12-week periods separated by a 3-week cross-over. With the exception of a single patient, the seizure count was lower during the lamotrigine phase. Of the patients recruited at study initiation, consisting of 30 consecutive patients evaluated at the referral centre, 20 had Lennox–Gastaut syndrome, and the responder group included 11 with Lennox–Gastaut syndrome, yielding a responder rate of 65% associated with this diagnostic group in the initial open-label phase.

In a trial that used a multicentre double-blind parallel-group design, lamotrigine was added on to the existing regimen in 58 patients (age range 2–55 years) with primarily generalized tonic–clonic seizures [137]. A greater than 50% reduction in the frequency of primary generalized tonic–clonic seizures occurred in 72% of patients during the 12-week maintenance phase, while 43% of 59 patients assigned to placebo had a greater than 50% seizure reduction, a statistically significant difference.

The efficacy of lamotrigine in the management of Lennox–Gastaut syndrome was shown in a pivotal double-blind, placebo-controlled add-on study [100]. A total of 169 patients were randomized to 16 weeks of treatment with lamotrigine ($n = 79$) or placebo ($n = 90$). The median monthly frequency of all major seizures decreased in the lamotrigine group from 16.4 to 9.9, compared with a seizure frequency change from 13.5 to 14.2 in the placebo group. A greater than 50% seizure reduction was seen significantly more often in the lamotrigine group (33% versus 16%).

In an uncontrolled study of 15 patients of mixed ages [138], when lamotrigine (1.6–3.0 mg/kg/day for children and 25–50 mg/day for adults) was added to valproic acid and continued for 3 months or longer, a total or near-total control of absence seizures was seen in 63% ($n = 9$).

Monotherapy studies in newly diagnosed absence seizures

The efficacy of lamotrigine monotherapy in patients with newly diagnosed childhood absence epilepsy was demonstrated in two studies.

In the first study, 30 of 42 patients (71%) aged 2 to 16 years became seizure free at a median dose of 5 mg/kg/day during a non-blind dose escalation phase [139]. In the subsequent double-blind, placebo-controlled phase restricted to patients who had responded to open-label treatment, significantly more patients remained seizure free in the group ($n = 15$) randomized to continue lamotrigine than in the group ($n = 14$) switched to placebo (62% versus 21%, respectively).

In the second trial, 38 children (3–13 years of age) were randomly assigned to lamotrigine or valproic acid according to an open-label design [140]. At 3 months, 63% of children taking valproic acid and 37% of those taking lamotrigine were controlled. After 12 months, 68% of children taking valproic acid and 53% taking lamotrigine remained seizure free. Valproic acid produced control of absence seizures faster, but the difference in efficacy at 12 months was not significant, possibly due to the limited sample size.

Monotherapy studies in newly diagnosed generalized and unclassifiable epilepsies

The efficacy and tolerability of lamotrigine, valproic acid and topiramate were compared in arm B of the SANAD study (n = 716), the design of which has been described above [134]. In this arm, which included patients with generalized and unclassifiable epilepsies, there was no significant difference between valproic acid and lamotrigine for time to treatment failure. Valproic acid, however, was better than lamotrigine for time to 12-month remission. Topiramate did not perform as well as the other AEDs in this study, largely due to inferior tolerability.

Meta-analyses of randomized controlled trials

In addition to a meta-analysis addressing the efficacy of adjunctive therapy with lamotrigine in refractory partial epilepsy [117], a pooled analysis of pivotal trial data focusing on seizure freedom indicated that lamotrigine was only infrequently associated with seizure-free outcome when added to an existing AED regimen in refractory epilepsy [141]. A series of meta-analyses also suggested lamotrigine to be possibly less effective than the most recently introduced AEDs in the treatment of refractory partial seizures [142,143]. When all available clinical trial data were utilized to compare lamotrigine with carbamazepine, a better tolerability of lamotrigine was confirmed, but comparison of efficacy data was judged inconclusive [144].

Other studies

A large number of experiential clinical studies have documented the place of lamotrigine in epilepsy treatment [47,99,101,145–158]. In an open study, for example, 21 patients (16–65 years old) with epileptic seizures of frontal lobe origin were maintained on a combination of lamotrigine and valproic acid [159]. At the end of 1 year, 17 patients continued on this combination and 10 had been free of clinical seizure recurrences. In other studies, lamotrigine was added on to existing AED regimens, and outcome measures were seizure remission and successful conversion to lamotrigine monotherapy. Treatment outcome of some epilepsy syndromes was quantitatively evaluated with EEG, particularly when the patient was unable to participate in the assessment [139,147,153,160–162]. Treatment-emergent adverse events were recorded and compared with the patient's treatment history as own control. Retention on lamotrigine suggested its clinical usefulness.

Successful applications of lamotrigine in refractory epilepsy have included conditions associated with underlying progressive neurological conditions, including refractory neonatal seizures [163], infantile spasms [164], Rett's syndrome [165] and juvenile neuronal lipofuscinosis [166].

There have been many studies to determine how long lamotrigine is retained during chronic use, mostly in patients with refractory epilepsies. In one study of longer than 3 years' duration, the proportion of patients retained on lamotrigine treatment was 29%, compared with 30% for topiramate and 10% for gabapentin [167]. Another multicentre study of 6 years' duration, in mostly difficult-to-treat patients, demonstrated a retention rate of somewhat less than 40% [168]. The same study demonstrated that fewer than 4% of the patients remained free of seizure recurrences. There also exists the need to better define the efficacy of lamotrigine in generalized epilepsies [168].

Quality of life assessments

A double-blind study compared lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure [169]. The population was identical to that of an already reviewed trial [131] that demonstrated a difference in study completion rate (lamotrigine 65% versus carbamazepine 51%). The modified Side Effect and Life Satisfaction (SEALS) inventory with five subscales (worry, temper, cognition, dysphoria and tiredness: a total of 20 points) was applied at weeks 4, 12, 24 and 48. The SEALS score worsened significantly at 4 weeks in the carbamazepine group, associated with deterioration in the cognition, dysphoria and tiredness subscales. Improvement observed among the carbamazepine group in the temper and worry subscales were smaller than those observed in the lamotrigine group. The SEALS score was better among the completers; worse scores at the baseline tended to predict dropout, and worsening of the SEALS score was actually seen, leading to dropout.

In another study, lamotrigine was added on to the treatment of 196 patients who had been receiving other AEDs, and the Profile of Mood States (POMS) and a 31-item Quality of Life scale (QOLIE-31) were applied at baseline [170]. Addition of lamotrigine was tolerated in 155 patients, and lamotrigine monotherapy was successfully established in 51 patients. The lamotrigine monotherapy group experienced an improvement in mood measures.

Paradoxical effects in myoclonus and myoclonic syndromes

Lamotrigine can aggravate myoclonus [171–175] and even precipitate myoclonic status [173], although improved control has also been reported in some cases [146]. Aggravation of severe myoclonic epilepsy in infancy (Dravet's syndrome) is particularly common with lamotrigine [174]. Myoclonus can represent a new symptom when lamotrigine is initiated in a patient with genetically determined forms of epilepsy [176,177]. The mechanisms involved in the differential exacerbation of myoclonus are unknown. There is a single case report of recurrent absence status epilepticus associated with lamotrigine therapy [178].

Use in non-epilepsy indications

A number of early reports of adverse events from clinical trials of lamotrigine in epilepsy concerned psychiatric symptoms compatible with elevation of mood. Subsequent clinical trials established the indication of lamotrigine in the maintenance treatment of bipolar I disorder and, in particular, bipolar depression [179,180]. A comprehensive review of the rapidly expanding lit-

erature on this topic is beyond the scope of this chapter. Lamotrigine has also been shown to be effective in the management of acute and chronic pain [181].

Adverse effects

Overview of the most common adverse effects

Assessment of the tolerability profile of lamotrigine has been complicated by its frequent use in combination with other AEDs [182,183]. Adverse events necessitated withdrawal of adjunctive lamotrigine therapy in 10.2% of patients participating in premarketing trials (n = 3501) [184]. Of these, skin rash was most frequently cited, and was responsible for discontinuation in 3.8% of patients. The most common adverse events associated with adjunctive lamotrigine use were primarily neurological, gastrointestinal and dermatological. In a placebo-controlled study of add-on lamotrigine (up to 500 mg/day) in 334 adults with partial epilepsy, dizziness (reported by 50% of lamotrigine patients), diplopia (33%), ataxia (24%), blurred vision (23%) and somnolence (14%) occurred significantly more frequently in the lamotrigine group than in the placebo group [185]. Skin rash was reported by 10% of lamotrigine patients, but the difference compared with the placebo group was not significant. Lamotrigine tolerability has been formally tested in maintenance doses up to 700 mg/day [186].

Information concerning the tolerability of lamotrigine alone can be derived from controlled studies of lamotrigine monotherapy. In comparative monotherapy trials in patients with newly diagnosed epilepsy, withdrawal rates were always lower with lamotrigine (4–15%) than with carbamazepine (10–42%), a difference mainly attributable to adverse events rates [122–124,126,128,129,131]. Withdrawal rates did not differ significantly between lamotrigine and gabapentin [128,130]. In two studies comparing lamotrigine and valproic acid in newly diagnosed patients, differences in rates of withdrawal from treatment were opposite in direction [124,125].

Pooled data from 536 patients with newly diagnosed epilepsy treated with lamotrigine monotherapy identified headache (18%), asthenia (15%), rash (11%), nausea (10%), dizziness (9%) and somnolence (8%) as the most frequent adverse events [122,123,126,129,131,132] (Table 43.6). When compared with carbamazepine and phenytoin, lamotrigine showed tolerability advantages in terms of a lower incidence of drowsiness. In fact, insomnia can be an adverse effect of lamotrigine [187]. Tolerability data available from studies comparing lamotrigine with gabapentin or valproic acid are more limited than those available for carbamazepine and phenytoin. When adverse events were compared between lamotrigine and gabapentin, weight gain was significant with gabapentin in both studies [128,130]. Valproic acid was definitely also more frequently associated with weight gain than lamotrigine [124,125].

Table 43.6 Adverse experiences often reported by newly diagnosed patients on lamotrigine monotherapy and active control groups.

Study	Lamotrigine, total [123,129,131,132]	Carbamazepine, total [123,129,131]	Phenytoin [132]
n	536	338	95
Daily dose	100–200 mg	600 or 400 mg	300 mg
Headache	99 (18%)	53 (17%)	18 (19%)
Asthenia	79 (15%)	69 (20%)	28 (29%)
Rash	57 (11%)	47 (14%)	9 (9%)
Nausea	51 (10%)	29 (9%)	4 (4%)
Sleepiness	43 (8%)	58 (17%)	27 (29%)
Dizziness	49 (9%)	43 (13%)	11 (12%)

Cognitive and psychomotor effects

Studies in healthy volunteers and patients with epilepsy have shown that lamotrigine causes fewer adverse psychomotor and cognitive effects than traditional AEDs. In contrast to diazepam (10 mg), carbamazepine (400–600 mg) and phenytoin (1000 mg), lamotrigine (120–300 mg) did not accentuate body sway and did not impair adaptive tracking (a measure of hand-to-eye coordination), smooth visual pursuit (a measure of cortical and cerebellar function) or saccadic eye movement (a measure of parapontine reticular formation function) after single oral doses in healthy volunteers [91,97]. Repeated doses of lamotrigine (mean 7.1 mg/kg/day for 4 weeks) did not affect psychomotor speed, sustained attention, verbal memory, language and mood measures in 17 healthy volunteers; in contrast, topiramate (5.7 mg/kg/day) significantly impaired attention and word fluency [188]. Similar results have been reported in other normal volunteer studies, when lamotrigine was tested against carbamazepine [189], valproic acid [190] and topiramate [191].

The absence of adverse cognitive effects of lamotrigine has been reported uniformly since earlier clinical studies [108,131,160], and these findings were confirmed in more recent controlled trials, when lamotrigine was added to pre-existing AED regimens [192,193]. In fact, one of the studies in healthy volunteers [190] demonstrated positive cognitive effects with lamotrigine.

Neurological and behavioural effects

A nationwide survey of patients in the UK evaluated the association between AED use and acute psychological disorders [194]. In 19 cases (30% of the total reported), the AED was considered to be responsible. Lamotrigine was implicated in three, and all three patients experienced interictal events, consisting of delirium in two and mood disorder in one. Schizophrenia-like psychotic symptoms were reported in six patients receiving lamotrigine for epilepsy [195]. Tourette's symptoms were provoked in a single patient with a bipolar disorder [196]. Additional neurobehavioural adverse experiences include aggression [197] and insomnia [187].

Sporadic reports suggest an association of lamotrigine use with chorea without a family history [198–200]. There is a single case report of downbeat nystagmus [201]. Dysgeusia has also been reported [202].

Neuroendocrine effects

In recent years, there has been increasing concern over the adverse effects of AEDs on neuroendocrine functions. Isojarvi *et al*. [203] were the first to direct attention to a possible contribution of valproic acid in the pathogenesis of polycystic ovarian syndrome.

The data from a double-blind randomized trial comparing lamotrigine with valproic acid monotherapy were analysed [204]. The patients were 12 years or older, consisting of 18 assigned to lamotrigine (doses of 100–500 mg/day) and 20 assigned to valproic acid (doses of 10–60 mg/kg). Among the adolescent patients (12–20 years old), body weight gain was more common in the valproic acid group during the 24 weeks of the maintenance phase, and the difference between the two groups was significant at 10 weeks. In another monotherapy comparison, there was a suggestion of a subclinical increase in the fasting insulin level in the valproic acid group, but only a small number of obese females had a polycystic ovarian syndrome [205]. Patients who had been on lamotrigine ($n = 119$) and valproic acid ($n = 103$) monotherapy for longer than 5 years were compared in an open-label study [206]. More lamotrigine patients (87%) than valproic acid patients (77%) reported regular menstrual cycles at the screening visit. The prevalence of anovulation did not differ between two groups. Mean total serum testosterone and androstenedione levels were significantly higher in the valproic acid group. Mean total insulin levels did not differ significantly.

Patients with epilepsy on AED treatment have been known to suffer impairments of sexual function. A study using a sexual function questionnaire reported improved sexual function when 79 male patients were initiated on lamotrigine monotherapy, or when 62 male patients were switched to lamotrigine because of unsatisfactory seizure control [207]. In another study, three groups of 25 male patients with partial epilepsy treated with phenytoin, carbamazepine and lamotrigine and 10 on no treatment were compared for sexual function scores (S-scores) and serum levels of dehydroepiandrosterone sulphate (DHEAS), bioactive testosterone, bioactive estradiol and bioactive androstenediol [208]. The lamotrigine group and the patients under no treatment were similar in S-scores and bioactive testosterone, and showed a more favourable sexual function profile than the carbamazepine and phenytoin groups.

There is a report of two children treated for diabetes insipidus who experienced an increase in desmopressin requirement when lamotrigine was added to treatment for their epilepsy [209].

Child development

In one study, concern was raised about reduced growth and bone mass in children with epilepsy receiving the combination of lamotrigine and valproic acid [210]. The effects of lamotrigine on physical maturation were evaluated more specifically in a group of 103 children over periods of 6–71 months [211]. The mean age at lamotrigine introduction was 6.7 years (1.6–16.4), and the mean daily lamotrigine dose was 7.4 mg/kg (range, 3.5–14.2 mg/kg). Long-term lamotrigine monotherapy was associated with normal body growth.

Idiosyncratic effects

Cutaneous reactions

Of all the adverse effects of lamotrigine, skin rash is one of the most significant. Many AEDs cause allergic skin rashes and lamotrigine is not unique [212]. Lamotrigine-induced skin rash has the typical characteristics of an allergic drug rash, and its incidence is higher in patients with a history of allergic skin rash in response to some other aromatic AEDs, and lower when a low starting dose and a slow dose escalation rate are used [213,214]. As lamotrigine use increased among paediatric populations, multiple clinical studies suggested that the incidence of lamotrigine-associated skin rash is higher in children than in adults [215–217]. In a retrospective review of 988 outpatient records, a skin rash was recorded in 56 (5.6%) and led to lamotrigine discontinuation in 39 (3.9%) [218]. A history of skin rash attributed to other AEDs increased the risk of a lamotrigine rash to 13.9%, compared with 4.6% in patients who had no such history. A younger age (<13 years) raised the risk from 4.3% to 10.7%. When two risk factors were present in the same patient, the risk of a lamotrigine-induced rash was 18.2%.

While there has been a report of non-maculopapular rash [219], lamotrigine-associated skin rash is typically maculopapular or erythematous, is associated with pruritus and has the characteristics of a delayed hypersensitivity reaction, appearing within the first 4 weeks of initiating treatment and resolving rapidly on drug withdrawal [220]. Rarely, the rash may be more severe (erythema multiforme) and progress to desquamation with involvement of the mucous membranes (Stevens–Johnson syndrome) and possibly to toxic epidermal necrolysis [221,222]. According to the manufacturer's product information [69], the incidence of serious skin rashes, including Stevens–Johnson syndrome, and rashes requiring hospitalization is approximately 8 per 1000 in patients younger than 16 years receiving lamotrigine as adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious skin rashes was 0.8 per 1000 in adults receiving lamotrigine as initial monotherapy and 1.3 per 1000 in adults receiving lamotrigine as adjunctive therapy.

Apparently, the pathophysiology of serious skin rashes is different from that of common allergic skin rashs, but its understanding must wait further studies [223]. In some patients, rash is accompanied by a flu-like syndrome of fever, malaise, myalgia, lymphadenopathy or eosinophilia, suggesting an immunological mechanism. No consensus exists as to which early dermatological features allow the clinician to differentiate potentially life-threatening from self-limited skin rash [224,225]. Specifically, reports from clinical trials indicated that as many as 1 in 100 to 1 in 50 paediatric patients developed a potentially life-threatening rash [216,226]. Conversely, the lamotrigine group did not differ significantly from the placebo group (9% versus 7%) in the incidence of any skin rash when elaborate dose escalation schedules were employed in a multicentre study of children with Lennox–Gastaut syndrome [100].

It is relevant that the US double-blind placebo-controlled study in children with refractory partial epilepsy [111] was carefully designed in terms of dose escalation schedule, and skin rash was a reason for withdrawal. No statistically significant difference in the incidence of skin rash emerged between the lamotrigine and placebo groups, but isolated cases of more severe skin rash occurred in the lamotrigine group. In a multicentre, non-randomized study, multiple dose escalation schedules included initial doses of 100, 25 and 12.5 mg/day in valproic acid-treated patients, and initial doses of 200 and 50 mg/day in carbamazepine- and phenytoin-treated patients [115]. When withdrawal rates due to skin rash were compared, the effect of a lower initial dose and a slower escalation was statistically significant only for

Table 43.7 Paediatric and adult rash rates with lamotrigine used alone and with different concomitant AEDs in clinical trials. In at least some of the groups included in early studies, rash rates were probably increased by excessively high dose escalation rates.

AED therapy	Total number of patients	All rash (%)	Rash leading to discontinuation (%)	Rash leading to hospitalization or Stevens–Johnson syndrome (%)[a]
Paediatric (younger than 16 years)				
Lamotrigine + enzyme-inducing AEDs	394	9.6	4.1	0.8
Lamotrigine + valproic acid + enzyme-inducing AEDs	155	4.5	0	0
Lamotrigine + valproic acid only	145	20.0	9.0	1.4
Lamotrigine + valproic acid + non-enzyme-inducing AEDs	145	21.4	10.3	1.4
Lamotrigine + other	60	11.7	3.3	0
Lamotrigine monotherapy	192	13.5	3.1	1.6
Adult (older than 16 years)				
Lamotrigine + enzyme-inducing AEDs	2240	6.7	2.0	0.1
Lamotrigine + valproic acid + enzyme-inducing AEDs	303	7.6	3.3	0.7
Lamotrigine + valproic acid only	205	19.5	12.2	2.0
Lamotrigine + valproic acid + non-enzyme-inducing AEDs	10	20.0	10.0	0
Lamotrigine + other	195	10.3	5.1	0.5
Lamotrigine monotherapy	420	14.5	6.0	0

From ref. 182 with permission.

[a] Hospitalization occurred more often for rash other than Stevens–Johnson syndrome.

the valproic acid group, in which 38%, 11% and 8% of patients discontinued treatment due to a rash for initial lamotrigine doses of 100, 25 and 12.5 mg/day respectively. A correlation between serum drug concentration and risk of skin rash at initiation of treatment had previously been noted with other AEDs [227]. More recent epidemiological data further suggested that there has been a reduction in the incidence of lamotrigine-associated serious skin rashes since lower starting doses and slower dose escalation rates were introduced, while the incidence of milder skin rashes has not changed [217,228].

There has been increasing recognition that the risk of skin rash is significantly increased when lamotrigine is initiated in patients already receiving valproic acid [222], but the risk can be reduced by using a slow escalation from a low starting dose [182,220] (Table 43.7).

It has been reported that lamotrigine withdrawal was not necessary in all patients who experienced skin rashes in clinical trials [138], as also suggested by a recent large retrospective review [218]. Some patients experiencing a skin rash at the initial exposure have been rechallenged later without recurrence of a rash [229,230], but any such rechallenges should be very cautious (and use very low starting dosages) to minimize the risk of serious reactions.

Other idiosyncratic reactions

Sporadic cases of multiorgan failure associated with disseminated intravascular coagulation have been reported. Multiorgan failure was initially attributed to status epilepticus [231] and/or concurrent serious systemic illnesses [184], but cases of multiorgan failure attributable to lamotrigine have also been reported [232–236]. Systematic analysis has suggested an overlap between multiorgan failure and a severe hypersensitivity syndrome associated with serious rash and fever [237].

There exist isolated reports of occurrences of pseudolymphoma [238], agranulocytosis [239], neutropenia [240] and hepatotoxicity [241]. The British postmarketing surveillance of adverse events associated with lamotrigine included rare single occurrences of hepatic failure, a severe flare-up of ulcerative colitis, disseminated intravascular coagulation and acute renal failure [167].

Sudden unexpected death in epilepsy

A total of 20 cases of sudden unexpected death in epilepsy (SUDEP) were reported among a cohort of 4700 patients with epilepsy (5747 patient-years of exposure) during the premarketing development of lamotrigine [69]. Retrospective analysis of the lamotrigine database indicated, however, that the risk of sudden death in lamotrigine-treated patients is no greater than that reported for other populations of people with epilepsy [242]. In a British postmarketing study, standardized mortality ratio was slightly higher than reported in the literature [167], but the result was interpreted to reflect the severity of epilepsy in the study population.

A 10-year series of consecutive SUDEP cases implicating lamotrigine as a possible causative factor was reported from one institution [243]. The four cases reported had been on long-term outpatient lamotrigine monotherapy, with serum lamotrigine concentrations between 7.0 and 27.5 mg/L prior to SUDEP.

A single case report of electrocardiographic QRS prolongation may be relevant [244]. The patient had been prescribed 200 mg lamotrigine and 600 mg felbamate, both three times daily, for epilepsy, and visited the emergency department following two clinical seizures. QRS prolongation (108 ms) was found and was immediately reversed to 98 ms with sodium bicarbonate administration. There was no evidence of acute intentional ingestion, and the lamotrigine serum concentration was 14.7 mg/L at presentation. Another single case report attributed QRS prolongation (110 ms) to lamotrigine [245]. Further investigations are needed, because lamotrigine may inhibit the cardiac rapid delayed rectifier potassium ion current, potentially rendering the patient at increased risk for cardiac arrhythmia [246].

Teratogenicity

Lamotrigine did not reveal significant teratogenic potential in preclinical animal testing. The manufacturer established a pregnancy registry and additional data about possible human teratogenicity of lamotrigine have been collected during routine clinical use [247].

As of March 2007, a total of 2622 pregnancies had been prospectively registered, with the pregnancy outcome known for 1741 and pending for 289 [248]. Exposure to lamotrigine monotherapy occurred in the first trimester in 1145 pregnancies. There were 23 live-born infants with major defects, three pregnancy terminations involving major defects and one fetal death with major birth defects, following earliest exposure to lamotrigine in the first-trimester. Following earliest exposure to lamotrigine monotherapy in the second trimester, four infants had major defects (62 total outcomes). There were 148 outcomes following first-trimester exposure to lamotrigine and valproic acid combined. Major birth defects were reported in 13, and there were two induced abortions with major birth defects. The first-trimester exposure to lamotrigine polytherapy without valproic acid was associated with 368 outcomes, eight infants with major birth defects, and one abortion with major birth defects.

While the sample size is still considered insufficient to reach definitive conclusions about the teratogenic risk of lamotrigine, a higher frequency of major malformations was seen in the group exposed to AED combinations including lamotrigine and valproic acid compared with lamotrigine monotherapy or other drug combinations. It is unclear, however, whether the higher frequency of major defects in the group receiving the valproic acid–lamotrigine combination can be ascribed to the independent teratogenic effects of valproic acid, or whether lamotrigine played a contributory role. Comparable results have been reported from a prospective UK Epilepsy and Pregnancy register [249].

Other studies discussing comparative teratogenicity data in women exposed to lamotrgine and other AEDs during pregnancy are discussed in Chapter 25.

Lamotrigine overdose

Sporadic cases of accidental or deliberate overdose of lamotrigine, involving quantities up to 15 g, have been reported, and some have been fatal. Observations from several cases of attempted suicide through ingestion of lamotrigine doses from 1350 to 4500 mg suggest that lamotrigine does not cause respiratory depression [245,250]. Recorded peak serum concentration varied from 18 to 53 mg/L. Reports to US poison centres during 2000 and 2001 included 493 lamotrigine cases, of which 173 (35.1%) were 5 years old or younger [251]. No toxic clinical effects were seen in 52.1%. Drowsiness, vomiting, nausea and ataxia were reported in 20.5%, 11%, 5.1% and 4.9%, respectively. Lamotrigine can induce seizures after acute injection [250,252]. Activated charcoal [245,250] can be used in the treatment of acute lamotrigine overdose.

Place in current therapy

Lamotrigine has been successfully tested as an effective therapeutic agent for a wide range of epilepsy syndromes, and the scope of its use is expected to continue to broaden. Treatment-emergent adverse experiences associated with its use have generally been limited to the period of dose escalation. It may not be the most effective of all AEDs, but it is highly acceptable for long-term use once its efficacy has been demonstrated and a maintenance dose has been determined in the individual patient. Clinicians are encouraged to attain monotherapy. Because of differences in lamotrigine pharmacokinetics related to type of co-medication, the dosing schedule at initiation of lamotrigine treatment depends on whether the patient is currently treated with valproic acid, enzyme-inducing AEDs or non-enzyme-inducing AEDs [182,253]. The flexibility of paediatric initiation and dosing has been appreciably improved by the introduction of lamotrigine in tablet sizes of 5 and 2 mg, and seems to have helped to reduce the incidence of skin rash. The manufacturer recommends the administration of whole tablets only. The dosing interval can be either once or twice daily, the latter being preferred in patients in whom the half-life is expected to be at the lower end of the reported range. An extended-release formulation is being developed to minimize fluctuations in serum lamotrigine concentrations during a dosing interval [52,114]. The manufacturer's updated recommendations for initial lamotrigine dose escalation are available online at http://us.gsk.com/products/assets/us_lamictal.pdf.

Dosing schedules for adjunctive use of lamotrigine in patients with epilepsy are given in Table 43.8 for subjects over 12 years of age and in Table 43.9 for subjects 2 to 12 years of age (with slight modifications from the US manufacturer's prescribing information, dated May 2007). A weight-adjusted dosing scheme for children (2 to 12 years of age) taking valproic acid is provided in Table 43.10. Drug interaction data indicate that in patients co-medicated with both valproic acid and enzyme-inducing AEDs, the opposing effects of these medications on serum lamotrigine levels cancel out virtually completely, resulting in lamotrigine pharmacokinetics comparable to those observed in patients on lamotrigine monotherapy (Table 43.3). It is, therefore, common practice, when the patient is currently receiving polytherapy including valproic acid and at least one enzyme-inducing AED, to employ the initial lamotrigine dosing schedule for 'patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate'.

Table 43.11 provides guidance for adjusting lamotrigine dose when converting from adjunctive lamotrigine therapy with valproic acid to lamotrigine monotherapy in patients over 16 years of age.

Initial monotherapy with lamotrigine is currently approved in the UK and many other countries for patients older than 12 years only. The dose titration rate recommendations for initiating lamotrigine monotherapy are identical to those for patients taking AEDs other than enzyme-inducing AEDs or valproic acid (Table 43.8), but seizure freedom in newly diagnosed patients can be maintained at doses appreciably lower than those derived from clinical trials involving refractory patients [254], and consideration of lower dosing for the elderly is appropriate [126,128,129]. In the USA, only conversion to lamotrigine monotherapy is approved.

Because of a faster rate of metabolism in children, children aged 2–6 years may require a maintenance dose at the higher end of the recommended range, especially when concomitant enzyme-

Table 43.8 Escalation regimen for lamotrigine in patients with epilepsy over 12 years of age.

	For patients taking valproic acid without enzyme inducers	For patients taking AEDs other than enzyme-inducing AEDs[a] or valproic acid[b]	For patients taking enzyme-inducing AEDs[a] and not taking valproic acid
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in two divided doses)
Week 5 onwards to maintenance	Increase by 25 to 50 mg/day every 1–2 weeks	Increase by 50 mg/day every 1–2 weeks	Increase by 100 mg/day every 1–2 weeks
Usual maintenance dose[c]	100–200 mg/day (one or two divided doses)	200–400 mg/day (in two divided doses) 100–200 mg/day (in two divided doses) for patients with newly diagnosed epilepsy started on initial monotherapy	300–500 mg/day (in two divided doses)

From ref. 69 with permission.

[a] Methsuximide, rifampicin, the lopinavir–ritonavir combination and oestrogen-containing contraceptive steroids have also been shown to increase the apparent clearance of lamotrigine.

[b] It is common practice to use this regimen also for patients started on lamotrigine monotherapy and for those receiving concomitant therapy with valproic acid plus at least one enzyme-inducing AED. Use for initial monotherapy is not currently approved in the USA.

[c] Lamotrigine maintenance doses were modified from the US manufacturer's prescribing information, which had been derived from the doses employed in placebo-controlled trials in refractory epilepsy.

Table 43.9 Escalation regimen for lamotrigine in patients with epilepsy, 2 to 12 years of age.

	For patients taking valproic acid without enzyme inducers	For patients taking AEDs other than enzyme-inducing AEDs[a] or valproic acid[b]	For patients taking enzyme-inducing AEDs[a] and not taking valproic acid
Weeks 1 and 2	0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet (see Table 43.10 for weight-based dosing guide)	0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet	0.6 mg/kg/day in two divided doses, rounded down to the nearest whole tablet
Weeks 3 and 4	0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet (see Table 43.10 for weight-based dosing guide)	0.6 mg/kg/day in two divided doses, rounded down to the nearest whole tablet	1.2 mg/kg/day in two divided doses, rounded down to the nearest whole tablet
Week 5 onwards to maintenance	The dose should be increased every 1–2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose	The dose should be increased every 1–2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose	The dose should be increased every 1–2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose
Usual maintenance dose	1–3 mg/kg/day (maximum 100 mg/day in one or two divided doses)	2.5 to 7.5 mg/kg/day (maximum 200 mg/day in two divided doses)	5–15 mg/kg/day (maximum 400 mg/day in two divided doses)
Maintenance dose in patients less than 30 kg	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response

[a] Methsuximide, rifampicin, the lopinavir–ritonavir combination and oestrogen-containing contraceptive steroids have also been shown to increase the apparent clearance of lamotrigine.

[b] It is common practice to use this regimen also for patients started on lamotrigine monotherapy (not approved up to 12 years) and for those receiving concomitant therapy with valproic acid plus at least one enzyme-inducing AED.

Table 43.10 Initial weight-based dosing guide for lamotrigine in patients with epilepsy aged 2 to 12 years and taking valproic acid (weeks 1 to 4).

If the patient's weight is . . .		Give this daily dose, using the most appropriate combination of lamotrigine 2-mg and 5-mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every *other* day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day

inducing AEDs are used. The safety and effectiveness of lamotrigine under 2 years of age has not been established and no dosage guidelines are available, but a lamotrigine dosing interval longer than 24 h has been successfully employed in infants prior to the availability of 2-mg tablets [255].

The highest maintenance dose reported in adults is 1900 mg daily [105]. In some patients, serum lamotrigine concentrations above 20 mg/L have been achieved during long-term treatment for epilepsy [107]. Even if rapid resumption of maintenance treatment may be desired in some patients in whom lamotrigine therapy has been stopped, the use of initial dose titration guidelines is recommended if lamotrigine has been discontinued for a

Table 43.11 Conversion from adjunctive lamotrigine therapy with valproic acid to lamotrigine monotherapy in patients with epilepsy ≥16 years of age.

	Lamotrigine	Valproic acid
Step 1	Achieve a dose of 200 mg/day according to guidelines in Table 43.8 (if not already on 200 mg/day)	Maintain previous stable dose
Step 2	Maintain at 200 mg/day	Decrease to 500 mg/day by decrements no greater than 500 mg/day per week and then maintain the dose of 500 mg/day for 1 week
Step 3	Increase to 300 mg/day and maintain for 1 week	Simultaneously decrease to 250 mg/day and maintain for 1 week
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day	Discontinue

period longer than five half-lives. A mean single oral lamotrigine loading at 6.5 mg/kg was evaluated in 24 patients in epilepsy monitoring units [256]: transient nausea was reported, but the target (maintenance) serum lamotrigine concentration was reached in 1–3 h. Replacement of lamotrigine with valproic acid can be performed by abrupt discontinuation of lamotrigine [257], but rapid lamotrigine withdrawal is not recommended without careful monitoring. Special cautions are recommended in optimizing lamotrigine therapy in patients with renal and hepatic disease [258], and lamotrigine dosing may require adjustment based on the degree of organ dysfunction (see section on Pharmacokinetics).

Routine monitoring of serum lamotrigine levels is not considered necessary [106,259,260] and dosage should be adjusted according to individual clinical response and tolerability. Serum drug level monitoring, however, may be indispensable in maintaining an individually tailored lamotrigine serum concentration through periods of alteration in lamotrigine pharmacokinetics discussed in this chapter, for example during pregnancy and puerperium and when potential interacting drugs are added or removed. While no other laboratory monitoring is recommended during lamotrigine treatment, clinical monitoring for adverse symptoms is important in view of rare reports of adverse systemic reactions.

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44 Levetiracetam

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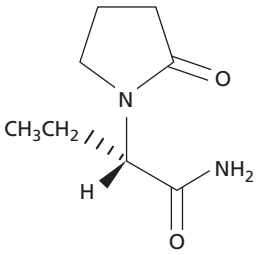

Primary indications	First-line and adjunctive therapy of partial-onset seizures. Adjunctive and, possibly, first-line therapy of generalized tonic–clonic seizures and myoclonic seizures associated with idiopathic generalized epilepsies. May also be valuable in the treatment of other generalized seizure types
Usual preparation	Immediate-release tablets: 250, 500, 750, 1000 mg Extended-release tablets: 500 mg, 750 mg Oral solution: 100 mg/mL Intravenous formulation: 500 mg/5 mL
Usual dosage	Adults: 1000–3000 mg/day. Treatment may be started with 500 or 1000 mg/day and increased to target dose by increments of 500 mg or 1000 mg every 1–2 weeks Children: 20–60 mg/kg/day. Treatment may be started at 10–20 mg/kg/day and adjusted, according to response, by increments of 10–20 mg/kg/day every 2 weeks
Dosing frequency	Twice daily
Significant drug interactions	Enzyme-inducing antiepileptic drugs decrease plasma levetiracetam levels by about 20–30%
Serum level monitoring	Dosage can usually be adjusted on the basis of clinical response. Monitoring serum levetiracetam levels may be useful in selected cases
Reference range	12–46 mg/L
Common/important adverse effects	Somnolence, asthenia, dizziness, ataxia, infection, nervousness, irritability, behavioural and psychiatric disorders
Main advantages	Relatively broad-spectrum activity, good tolerability and lack of clinically significant drug interactions
Main disadvantages	Efficacy in some generalized seizure types and epilepsy syndromes unproven. Behavioural and psychiatric adverse effects
Mechanism of action	Binds to synaptic vesicle 2A (SV2A) protein
Oral bioavailability	Complete
Time to peak levels	0.5–2 h (2–10 h with extended-release tablets)
Elimination	Primarily by urinary excretion in unchanged form. About 24% of the dose undergoes hydrolysis to LO57. Minor oxidized metabolites account for about 3% of urinary recovery
Volume of distribution	0.5–0.7 L/kg
Elimination half-life	6–8 h

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Plasma clearance	0.9–1.3 mL/min/kg (values in the upper range for patients co-medicated with enzyme inducers). Clearance is faster in children and slower in the elderly
Protein binding	<10%
Active metabolites	None known
Comment	A valuable antiepileptic drug for both first-line use and adjunctive therapy

Introduction

The antiepileptic drug (AED) levetiracetam is a pyrrolidine derivative that differs from all other currently approved AEDs in its chemical structure, pharmacological profile and mechanism of action, and as a consequence possesses unique pharmacological properties. Levetiracetam was first approved in the USA in 1999 as adjunctive treatment in patients with partial-onset seizures, and subsequently gained approval for this and other indications in many countries around the world. This chapter will review preclinical data, efficacy, safety and clinical use.

Chemistry

Levetiracetam is a white to off-white crystalline powder that is highly soluble in water (104.0 g/100 mL) and freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL). Its chemical name is (–)(*S*)-α-ethyl-2-oxo-1-pyrrolidine-acetamide and its chemical structure can be found in the summary table on the opening page of this chapter. Its molecular weight is 170.21. Levetiracetam is a racemically pure S-enantiomer [1]. The R-enantiomer has been shown to be devoid of anticonvulsant properties in animal models of epilepsy [2].

Pharmacology

Activity in experimental models of seizures and epilepsy

Unlike other AEDs, levetiracetam is not active in standard animal screening models which rely on production of an acute seizure, such as the maximal electroshock and the subcutaneous pentylenetetrazole model [3], which had previously been thought to reliably identify compounds endowed with antiepileptic effects in man. Levetiracetam does not show protective activity in a variety of maximal chemoconvulsive seizure models in mice, including seizures induced by the excitatory amino acids *N*-methyl-D-aspartate (NMDA), kainic acid and α-amino-3-hydroxy-5-methyl-4-isoxazolone propionate (AMPA), as well as bicuculline, picrotoxin and 3-mercaptopropionic acid [4]. However, it is active against seizures induced by pilocarpine and kainic acid in rats, which mimic human partial seizures with secondary generalization. Despite its unusual and mostly inactive profile in acute seizure models, levetiracetam is active in a variety of animal models that are felt to mimic chronic epilepsy, such as the amygdala kindling model in rats and pentylenetetrazole kindling in mice [4]. One study [5] demonstrated that levetiracetam is effective in a subset of amygdala-kindled rats which are resistant to phenytoin, suggesting that levetiracetam might be useful in patients who had been treatment resistant in the past. Levetiracetam is also effective in genetic animal models that resemble human spike–wave conditions, including the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) [6].

Levetiracetam is also effective in delaying the acquisition of amygdala kindling in rats and corneal and pentylenetetrazole kindling in mice [2,7]. This is felt to signal a potential antiepileptogenic effect, which is not present for many standard AEDs. Phenytoin and carbamazepine do not delay acquisition of kindling, although valproic acid and phenobarbital do. However, levetiracetam is the only one of these three drugs that delays acquisition of kindling at doses that are devoid of adverse effects [4].

Some experiments indicate a potential for the development of tolerance in the amygdala-kindled rat model, but no tolerance was observed in a chronic mouse model of epilepsy or in a bicuculline rat model [4,8,9]. Of note, a recent experiment in chronically seizing rats demonstrated that levetiracetam infusion produced complete suppression of seizures in the first 3 days, after which seizures gradually returned to baseline frequency, despite continuously elevated brain concentrations of the drug [10]. A 2-week hiatus in treatment led to a return of effect. The significance of these disparate findings remains to be determined. Levetiracetam is not considered to be a substrate for the P-glycoprotein multidrug transporter [11].

In preclinical safety tests, levetiracetam did not produce motor impairment in the Rotarod test in rats and mice, except at very high levels, and did not cause obvious sedation in the open-field test [3,4]. In both the kindling model and the GAERS model, there was a wide safety margin between the effective dose and the neurotoxic dose. Levetiracetam, in contrast to other AEDs, did not demonstrate an increase in neurotoxicity when used in kindled animals compared with control animals [4]. Levetiracetam did not produce cognitive impairment in the Morris water maze test in rats, whereas carbamazepine, valproic acid and clonazepam did [12].

Mechanisms of action

The mechanism of action of levetiracetam differs from that of other AEDs and appears to be mediated by binding to the synaptic vesicular protein SV2A [13]. The precise mechanism by which this binding produces an anticonvulsant effect is unknown, but it is likely to involve inhibition of neurotransmitter release from end

terminals. There is a strong correlation between binding affinity at this site and anticonvulsant potency as measured in a number of animal models, including the mouse audiogenic seizure model, the mouse corneal kindling model and the GAERS rat [14].

The binding of levetiracetam to SV2A can be displaced by piracetam, ethosuximide and pentylenetetrazole, but not by commonly used AEDs such as phenytoin and carbamazepine [15]. Levetiracetam's action does not involve any of three main mechanisms underlying the effects of classical AEDs (i.e. blockade of sodium and T-type calcium channels and enhancement of GABAergic neurotransmission) [16]. Some studies suggest that levetiracetam moderately inhibits N-type calcium channels and opposes the inhibitory action of zinc on GABA- and glycine-gated currents [16]. It is unclear whether these mechanisms have a role in its antiepileptic action. Levetiracetam inhibits burst firing without affecting normal neuronal excitability [17,18]. This appears to relate to a novel ability to inhibit hypersynchronization of epileptiform activity, which distinguishes levetiracetam from other AEDs [19].

Pharmacokinetics

Levetiracetam shows linear pharmacokinetics. The pharmacokinetic profile of the drug has been studied in healthy adults, in adults and children with epilepsy, in elderly subjects and in subjects with renal and hepatic impairment.

Absorption

Immediate-release tablets

Levetiracetam is rapidly and virtually completely absorbed after oral administration of immediate-release tablets, with an absolute oral bioavailability close to 100%. Peak plasma concentrations (C_{max}) are reached in 0.5–2 h [20,21]. Administration with food does not reduce the extent, but slows the rate of absorption [20]. Administering the immediate-release tablets after crushing and mixing them with apple sauce or enteral nutritional formulas slightly reduced C_{max}, but not significantly so [22].

Oral solution

The pharmacokinetic profile for the 10% oral solution of levetiracetam is essentially identical to that of the tablet formulation. Because the solution is bioequivalent to the tablets, no adjustment in dosage is necessary if a patient is switched from one formulation to another [23].

Extended-release formulation for once-daily administration

An extended-release formulation has been designed to be administered once a day. After administration of levetiracetam extended release under fasting conditions, median time to peak is delayed by approximately 3 h compared with the immediate-release formulation (4 h versus 0.9 h, respectively). At a dosage of 1000 mg/day, the average steady-state plasma concentration was 12.9 mg/L [coefficient of variation (CV) = 13%] with levetiracetam extended release given once daily and 13.6 mg/L (CV = 16%) with immediate-release tablets given twice daily, and the two regimens were bioequivalent [24]. The absorption of the extended-release formulation is not modified by food intake [24].

Intravenous formulation

Levetiracetam is available as an intravenous formulation (100 mg/mL), to be administered as a 15-min infusion. A 1500-mg intravenous infusion is bioequivalent to the oral formulation (three doses of 500-mg tablets) and steady-state conditions are achieved in 48 h with twice-daily intravenous dosing [21]. Pharmacokinetic modelling using adult intravenous and paediatric oral data indicate that a 15-min infusion should also be optimal for paediatric populations [25]. Approval of the intravenous use in children was granted in the European Union on this basis, without formal paediatric trials.

Distribution

The volume of distribution of levetiracetam is similar to intracellular and extracellular water, at 0.5–0.7 L/kg. Despite its water-soluble nature, levetiracetam readily and freely crosses the blood–brain barrier [26]. Levetiracetam also crosses the placenta, and fetal plasma levels approximate maternal levels. Levetiracetam is also excreted in breast milk at concentrations comparable to those in maternal plasma [27,28].

Levetiracetam is <10% bound to plasma proteins [29]. Saliva and plasma concentrations are similar, as shown in children [30] and in adults [31].

Elimination

Overall, 66% of an orally administered dose of levetiracetam is excreted unchanged in the urine. Most of the remainder (24%) is metabolized by enzymatic hydrolysis of the acetamide group to the corresponding carboxylic acid ucb L057 [20], which has no known pharmacological activity. Hydrolysis occurs diffusely in different tissues. Conversion to minor oxidized metabolites accounts for about 3% of urinary recovery.

In healthy volunteers, the apparent total body clearance of levetiracetam across studies is around 70 mL/min (1 mL/min/kg) on average. The half-life of levetiracetam in adults is approximately 6–8 h. However, since the mechanism of action is unclear, this may not necessarily reflect the functional half-life, and indeed there is evidence from studies of the effect on the photoparoxysmal response that the duration of effect (up to 30 h, after single 250- to 750-mg doses) may be much longer than the drug's half-life [32]. It was on this basis that a twice-daily regimen was selected for clinical trials.

Pharmacokinetics in special populations

Ethnic groups

The pharmacokinetics of levetiracetam has been evaluated in Asians of both Chinese and Japanese descent, and appears to be similar to that in whites, when differences in body weight are taken into account [33,34].

Infants and children

Levetiracetam pharmacokinetics has been assessed in infants and children with epilepsy in a variety of studies [30,35–37]. Follow-

ing a single oral dose of 20 mg/kg in 24 children aged 9.4 ± 2.2 years, the average plasma clearance of levetiracetam was 1.43 ± 0.36 mL/min/kg and the average half-life was 6.0 ± 1.1 h [36]. At steady state with 20 mg/kg twice-daily dosing in 14 children aged 10.2 ± 2.2 years, the mean plasma clearance was 1.10 ± 0.16 mL/min/kg and the mean half-life was 4.9 ± 0.4 h [30]. In a third study, 13 infants and young children aged 19.9 ± 14.16 months (range 2.3–46 months) received a single dose of 20 mg/kg, and the mean clearance and half-life were 1.46 ± 0.42 mL/min/kg and 5.3 ± 1.3 h respectively [35]. Overall, these results suggest that levetiracetam clearance, normalized for body weight, is about 20–45% greater in infants and children than in adults.

Population pharmacokinetics was used to analyse pooled data collected from 228 children with epilepsy aged 3 months to 18 years [37]. The main explanatory variables were the influence of age on the absorption rate, of body weight on clearance and on distribution volume, and of enzyme-inducing AEDs on clearance, body weight being the most influential covariate. Concomitant use of enzyme-inducing AEDs lowered the plasma concentrations of levetiracetam by about 20%. Simulations were performed to identify dosing regimens achieving steady-state peak and trough plasma levetiracetam concentrations similar to those attained in adults receiving a dose of 500 mg twice daily, the recommended starting dose for adjunctive therapy in the product information sheet. It was concluded that, to achieve these concentrations, dosing can be carried out with either 10 mg/kg of oral solution twice daily in children weighing <50 kg and a 500-mg tablet twice daily in those weighing >50 kg or, when patients favour a solid formulation, 10 mg/kg of oral solution twice daily in children weighing <20 kg, a 250-mg tablet twice daily in those weighing 20–40 kg, and a 500-mg tablet twice daily in those weighing >40 kg. As in adults, this dose could be adjusted based on the individual efficacy and tolerability within the range of 10–30 mg/kg twice daily.

Pregnancy and perinatal period

The pharmacokinetics of levetiracetam was investigated in women with epilepsy receiving levetiracetam treatment during pregnancy and lactation, as well as in neonates born to these women [27]. In 12 pregnant women, levetiracetam apparent oral clearance was significantly increased from 87 ± 40 mL/min at baseline to 297 ± 147 mL/min during the third trimester, implying that at unchanged doses the plasma concentration of the drug decreases by a mean of about 70% between baseline and the third trimester. At delivery, the concentration of levetiracetam in neonatal cord blood approximated maternal plasma concentration (mean ratio 1.09, range 0.64–2.0). However, neonatal plasma concentrations declined to 20% of maternal levels within 36 h, despite the fact that most infants were breastfed. Neonatal elimination half-life was 18 h [27]. Concentrations of levetiracetam in breast milk were similar to maternal plasma concentrations, and no accumulation was found in the plasma of breastfed infants [27,28]. Plasma concentrations of levetiracetam in these infants were about 13% of those seen in the mothers.

A marked decline in plasma concentration of levetiracetam during pregnancy, followed by a rapid increase after delivery, has been confirmed in another study [38]. In 11 women, the mean plasma concentration–dose ratio in the third trimester of pregnancy was only one-half of the mean concentration–dose ratio at baseline.

Table 44.1 Levetiracetam dosing in patients with renal impairment.

Renal function	Creatinine clearance (mL/min/1.73 m^2)	Dose administered twice daily (mg)
Normal	>80	500–1500
Mild	50–80	500–1000
Moderate	30–50	250–750
Severe	<30	250–500

From ref. 41 with permission.

The elderly

In a study based on therapeutic drug monitoring data, levetiracetam apparent oral clearance was compared in the youngest (16–31 years; $n = 151$) and oldest (55–88 years; $n = 157$) quartile of a population of 629 adult outpatients receiving levetiracetam therapy [39]. On average, clearance was 40% lower in older patients than in younger patients (46.5 versus 78.3 mL/h/kg, respectively). In another study conducted in 16 hospitalized elderly patients, levetiracetam exhibited a prolonged half-life, which could be explained entirely by reduced creatinine clearance [40]. The elimination half-life was approximately 10–11 h, compared with 7.7 h in younger normal subjects [20]. Adjustments in dosage in elderly patients should be made based on estimated creatinine clearance, taking body surface area into account.

Renal impairment

As might be expected, renal impairment reduces the clearance of levetiracetam and its metabolites. Compared with values recorded in subjects with normal renal function, levetiracetam clearance is reduced on average by 40% with a creatinine clearance (CL_{Cr}) of 50–80 mL/min, by 50% with CL_{Cr} of 30–50 mL/min, and by 60% with $CL_{Cr} < 30$% [20,41]. Dose reductions in relation to the degree of renal impairment are recommended, as outlined in Table 44.1. For patients with renal failure on dialysis, a dose of 500–1000 mg/24 h is recommended, with a supplemental dose of 250–500 mg after a dialysis treatment [20].

Hepatic impairment

The disposition of levetiracetam has been investigated in subjects with various stages of hepatic impairment. Mild to moderate (Child–Pugh class A or B) hepatic impairment did not alter the clearance of levetiracetam, and no dosage adjustments are required in these patients. However, levetiracetam clearance was reduced in severe hepatic failure (Child–Pugh class C), most likely due to concomitant renal insufficiency [42]. Adjustments in dose should therefore be made based on renal rather than hepatic function.

Drug interactions

A study using human liver microsomal enzymes revealed no inhibitory effects of levetiracetam on drug-metabolizing enzymes,

including CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2E1, CYP2D6, epoxide hydrolase and various uridine glucuronyltransferases [43]. Because the major metabolic pathway of levetiracetam is not cytochrome P450 dependent, and because levetiracetam does not induce or inhibit drug-metabolizing enzymes, interactions between levetiracetam and other drugs are considered unlikely. However, because unpredictable interactions may occur, specific investigations were performed with commonly used agents.

Effect of other drugs on levetiracetam pharmacokinetics

Two population pharmacokinetic analyses conducted in adults [33,44,45] and in children [37] showed that concomitant use of enzyme-inducing AEDs led to an increase of about 20% in levetiracetam clearance. In another study, co-medication with an enzyme-inducing AED, mostly carbamazepine, was associated with a 24% increase in levetiracetam clearance [39]. In a small number of patients who were studied on and off concomitant enzyme-inducing AEDs, however, levetiracetam clearance was 37% higher while enzyme inducers were co-administered [39]. At least for the majority of patients, no adjustments in levetiracetam dosage are expected to be required when enzyme-inducing AEDs are added or withdrawn.

Probenecid increases the plasma levels of the levetiracetam metabolite ucb L057 2.5-fold, by inhibiting renal tubular excretion, but does not affect the pharmacokinetics of the parent drug [20].

Effect of levetiracetam on the pharmacokinetics of other drugs

When up to 2000 mg/day levetiracetam was added on in patients receiving monotherapy with phenytoin (n = 6), carbamazepine (n = 4), valproic acid (n = 6) or a combination of carbamazepine and valproic acid (n = 2), there were no changes in plasma levels of the background drugs [46]. Another small study of 17 refractory epilepsy patients found no effect of levetiracetam on the plasma levels of carbamazepine, phenobarbital, valproic acid, primidone and clobazam [47]. In this study, there was a variable change in plasma phenytoin levels when levetiracetam was added. This potential interaction was specifically investigated in a subsequent study [48]. Tracer doses of deuterium-labelled phenytoin were given intravenously before and 12 weeks after adding on levetiracetam to the regimen of patients initially taking phenytoin as monotherapy. Phenytoin pharmacokinetic parameters did not change after adding levetiracetam. The authors concluded that levetiracetam does not affect phenytoin disposition.

The potential influence of levetiracetam on the pharmacokinetics of other AEDs was also assessed during randomized controlled trials. Plasma levels of concomitant AEDs were not significantly altered in any of the placebo-controlled adjunctive trials of levetiracetam or in a pooled analysis in adults and in children [44–45,49–52].

In interaction studies with oral contraceptives digoxin and warfarin, no evidence of any specific interaction between levetiracetam and these agents could be demonstrated [43].

Serum level monitoring

Plasma or serum concentrations of levetiracetam have been determined using gas chromatography with nitrogen phosphorus detection [29], high-performance liquid chromatography with ultraviolet detection [53] or liquid chromatography with mass spectrometric detection [54].

Levetiracetam exhibits moderate intra- and interindividual variability in pharmacokinetics, compared with other AEDs. However, due to its relatively short half-life, coupled with the common practice of twice-daily administration, plasma concentrations will vary over the course of the day, depending on temporal relationship to the last dose. Thus, if monitoring is performed for the purpose of measuring compliance, it should be done at the same time in relation to dose (usually trough levels). In patients who benefit from levetiracetam therapy, plasma concentrations in the range of 8–40 mg/L have been reported [55,56]. In a recent position paper published by a subcommittee of the International League Against Epilepsy, the reference range for plasma levetiracetam concentrations was set at 12–46 mg/L, although it was emphasized that individual patients may require concentrations outside this range [57].

To date, the clinical utility of monitoring plasma levetiracetam levels has not been established, but there are reasons to expect that concentration measurements may be valuable in selected situations, such as a check for compliance or when clinically important changes in plasma concentrations are expected (e.g. before and during pregnancy, and during puerperium). It is recommended that the blood be centrifuged within a short time frame after sampling, so as to avoid levetiracetam hydrolysis *in vitro* that would result in spuriously lower concentrations being measured [58].

Efficacy

Adjunctive therapy in refractory partial seizures in adults

Studies with the conventional formulation

Levetiracetam has been demonstrated to be effective in reducing the frequency of partial-onset seizures in patients with treatment-resistant epilepsy in three randomized controlled studies [50–52]. The characteristics of these studies can be found in Table 44.2. A total of 904 subjects were randomized to placebo or levetiracetam 1000 mg/day, 2000 mg/day or 3000 mg/day. Results from these studies showed that levetiracetam-treated patients had significantly fewer seizures than placebo-treated patients, as measured by the responder rate (proportion of patients with ≥50% reduction in weekly seizure frequency from baseline) and percent reduction in seizure frequency.

In a fourth study, also summarized in Table 44.2, patients with fewer refractory partial-onset or primary generalized tonic–clonic seizures (eligibility criteria allowed inclusion of patients with low seizure frequency, that is up to four seizures during the 24 weeks prior to enrolment) were randomized to placebo, 2000 mg/day levetiracetam or 4000 mg/day levetiracetam, started without titration [49]. Responder rates were higher

Table 44.2 Randomized placebo-controlled trials of levetiracetam as adjunctive therapy in adults with partial-onset seizures.

Study	*n*	Design	Inclusion criteria	Doses	Treatment duration	Percentage responders (patients with ≥50% seizure reduction). *P*-values refer to each levetiracetam group compared with placebo	Percentage seizure free for full study duration
Shorvon [51]	324	Double-blind randomized parallel	Refractory partial seizures; ≥4 seizures/4 weeks; one or two concomitant AEDs	1000 mg, 2000 mg	12 weeks	Placebo: 10.4% 1000 mg: 22.8%, $P = 0.019$ 2000 mg: 31.6%, $P < 0.001$	Placebo: 9% 1000 mg: 5% 2000 mg: 2%
Ben-Menachem [52]	286	Double-blind randomized parallel group followed by responder-selected	Partial seizures; 2 or more seizures/4 weeks; one concomitant AED	3000 mg	18 weeks (add-on phase only)	Placebo: 16.7% 3000 mg: 42.1%, $P < 0.001$	Placebo: 1.0% 3000 mg: 8.2%
Cereghino [50]	294	Double-blind randomized parallel	Refractory partial seizures; ≥12 seizures/12 weeks; one or two concomitant AEDs	1000 mg, 3000 mg	18 weeks	Placebo: 10.8% 1000 mg: 33.0%, $P < 0.001$ 3000 mg: 39.8%, $P < 0.001$	Placebo: 0.0% All levetiracetam doses: 5.5%
Betts [49]	119	Double-blind randomized parallel group	Refractory partial seizures;[a] ≥4 seizures/24 weeks; one to three concomitant AEDs	2000 mg, 4000 mg[b]	24 weeks	Placebo: 16.1% 2000 mg: 28.6%, $P = 0.01$ 4000 mg: 48.1%, NS	Placebo: 2.5% 2000 mg: 9.5% 4000 mg: 5.2%

[a] Also included patients with primarily generalized tonic–clonic seizures.
[b] No titration was used in this study.

with levetiracetam 2000 mg/day (48.1%, $P < 0.05$, $n = 27$) and 4000 mg/day (28.6%, NS, $n = 28$) than with placebo (16.1%, $n = 31$). When all patients were converted to 4000 mg/day in a non-blinded extension phase, no additional efficacy was gained (46.2% responder rate in patients initially treated with 2000 mg/day versus 39.3% in patients initially treated with 4000 mg/day).

Pharmacological modelling of seizure count data from the four trials led to the conclusion that about three-quarters of patients on levetiracetam exhibited a reduced seizure frequency from baseline [59]. There was a significant relationship between dose and seizure frequency reduction from baseline, characterized by an ED_{50} of 1408 mg/day. Age, gender, body weight, race and number of concomitant AEDs affected neither the percentage of improving patients nor the extent of change in seizure frequency from baseline.

A Cochrane review [60] demonstrated that the overall odds ratio (OR) for levetiracetam versus placebo for responder rates across the four double-blind placebo-controlled studies described above was 3.81 [95% confidence interval (CI) 2.78–5.22]. The review provided clear evidence for levetiracetam's efficacy, with an increase in effect with increasing dose within the 1000–3000 mg/day dose range.

A pooled analysis investigated seizure freedom rates. When seizure freedom was defined as the absence of seizures during the stable dose period, and withdrawals were counted as not seizure free, seizure freedom rates were 0.8%, 4.7%, 6.3% and 8.2% for placebo and levetiracetam 1000 mg/day, 2000 mg/day and 3000 mg/day, respectively [61].

In a retrospective pooled analysis, a fast onset of action was demonstrated within the first weeks of treatment in patients with partial-onset seizures [62]. With respect to long-term efficacy, Zaccara *et al.* [63] reviewed eight open-label long-term studies in adults with refractory, mostly partial-onset, seizures in whom levetiracetam was added to a previous treatment. Selected studies reported or allowed the calculation of the number of patients who achieved seizure freedom for 6 months and/or the number of patients withdrawing for adverse effects and/or the number or percentage of patients continuing treatment after 1 year. The results showed that the total percentage of patients who experienced 6 months' seizure freedom was 13.2% (95% CI 11.8–14.6). After 1 year of treatment, levetiracetam retention rates, a combined estimate of efficacy and safety, ranged from 60% to 75%.

Studies with the extended-release formulation

A double-blind, placebo-controlled study demonstrated the efficacy and tolerability of once-daily dosing with 1000 mg (two doses of 500-mg tablets) levetiracetam extended release as add-on therapy in patients (12–70 years old) with refractory partial-onset seizures uncontrolled on one to three AEDs [64]. After an 8-week prospective baseline, patients were randomized to levetiracetam extended release ($n = 79$) or placebo ($n = 79$) for 12 weeks without titration. The median per cent reduction in partial-onset seizure frequency per week on levetiracetam extended release was 46.1% compared with 33.4% on placebo. The estimated per cent reduction over placebo in seizure frequency per week over the treat-

ment period was 14.4% in the intent-to-treat (ITT) population ($P = 0.038$). Overall, 43% of patients on levetiracetam extended release were responders compared with 29.1% of patients on placebo. Among subjects who completed the 12-week treatment, 8/79 (10.1%) patients on levetiracetam extended release and 1/79 (1.3%) on placebo were free of partial-onset seizures during the treatment period.

Adjunctive therapy in refractory partial seizures in children

A randomized placebo-controlled trial assessed the efficacy of levetiracetam as adjunctive therapy in children (4–16 years of age) with treatment-resistant partial-onset seizures [65]. A total of 198 children were randomized and provided evaluable data. The starting dose of 20 mg/kg/day was up-titrated to a target dose of 60 mg/kg/day. A ≥50% reduction in partial seizure frequency per week was attained in 44.6% of patients (45/101) in the levetiracetam group, compared with 19.6% of patients (19/97) in the placebo group ($P = 0.0002$). Seven (6.9%) levetiracetam-treated patients were seizure free during the entire 14-week double-blind treatment period, compared with one (1.0%) placebo-treated patient. Of 192 patients who completed the short-term phase, 183 entered a long-term phase.

A multicentre, double-blind, randomized, placebo-controlled, parallel-group, adjunctive therapy inpatient study assessed the efficacy and safety of levetiracetam oral solution (20–50 mg/kg/day) in infants and children (1 month to less than 4 years of age) with partial-onset seizures. The study consisted of a 5-day evaluation period that included 1 day's up-titration. The average daily seizure frequency was calculated from a 48-h screening video-EEG assessment over the last 2 days of the evaluation period. Video-EEGs were read by an experienced reader who was blinded to treatment groups. The ITT population included 116 patients randomized, and the modified ITT population included 109 (58 levetiracetam, 51 placebo) patients, representing all ITT subjects who completed the baseline video-EEG and at least 24 h of the evaluation video-EEG, plus any randomized subjects who withdrew before the first 24 h of the evaluation video-EEG for reasons linked to lack or loss of efficacy. The responder rate was significantly greater for levetiracetam (43.1%) than for placebo (19.6%; $P = 0.013$), with consistent results across all age categories (1 month to <1 year; 1 year to <2 years; 2 years to <4 years) [66].

Monotherapy in partial-onset seizures

One double-blind, randomized, placebo-controlled study evaluated levetiracetam as monotherapy after conversion from adjunctive treatment in refractory patients with partial-onset seizures [50]. A total of 286 patients entered an initial double-blind randomized 18-week phase during which they received add-on levetiracetam (3000 mg/day, $n = 181$) or placebo ($n = 105$). The 86 patients who had a ≥50% reduction in seizure frequency (whether on placebo or levetiracetam) during the randomized add-on phase underwent a 12-week gradual taper of their background AED, after which they entered a 12-week monotherapy phase. Patients exited the study if they had worsening of seizures, as measured by pre-established criteria. By the end of the study, 19.9% (36/181) of patients initially randomized to levetiracetam were able to complete the study, compared with 9.5% (10/105) of placebo patients. Nine of the 49 patients who were successfully down-titrated to levetiracetam monotherapy were seizure free.

Another monotherapy study was performed in patients with newly diagnosed epilepsy [67]. In this study, levetiracetam was compared with controlled-release carbamazepine at optimized dosages in a non-inferiority designed trial, which was the first study to comply with European regulations for the evaluation of a new AED in pursuit of a monotherapy indication. Adults with two or more partial-onset or generalized tonic–clonic seizures in the previous year (excluding patients with clinical or EEG evidence suggestive of idiopathic generalized epilepsy) were randomly assigned to levetiracetam (500 mg twice daily, $n = 288$) or controlled-release carbamazepine (200 mg twice daily, $n = 291$). Dosage was adjusted stepwise based on seizure recurrence up to an intermediate (levetiracetam 2000 mg/day; carbamazepine 800 mg/day) or up to the maximum daily dose (levetiracetam 3000 mg/day or carbamazepine 1200 mg/day). Patients achieving the primary endpoint (6 months' seizure freedom) continued on treatment for a further 6-month period. At per-protocol analysis, 73.0% (56.6%) of patients randomized to levetiracetam and 72.8% (58.5%) of those randomized to carbamazepine were seizure free for 6 months (1 year) at the last evaluated dose (adjusted absolute difference for the primary endpoint 0.2%; 95% CI 7.8–8.2%). Because the lower limit of the 95% CI for the adjusted absolute difference for the primary endpoint was above the non-inferiority limit set by the study protocol (–15%), levetiracetam could be considered non-inferior to controlled-release carbamazepine. Of all patients achieving 6-month (1-year) seizure freedom, 80.1% (86.0%) in the levetiracetam group and 85.4% (89.3%) in the carbamazepine group did so at the lowest dose level (levetiracetam 1000 mg/day; carbamazepine 400 mg/day). More than 50% of the patients who were escalated to the intermediate (levetiracetam 2000 mg/day; carbamazepine 800 mg/day) or highest (levetiracetam 3000 mg/day; carbamazepine 1200 mg/day) doses responded to treatment. Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy at optimal dosing in a setting mimicking clinical practice.

Adjunctive therapy in refractory generalized epilepsies

The first randomized placebo-controlled trial of levetiracetam in patients with idiopathic generalized epilepsy with myoclonic seizures evaluated the efficacy and safety of a 3000 mg/day dose as adjunctive therapy in 120 subjects (12–65 years old) diagnosed with either juvenile myoclonic epilepsy (93.4%) or juvenile absence epilepsy (6.6%) [68]. The response rate during the 16-week treatment period (reduction of ≥50% in the number of days/week with myoclonic seizures) was 58.3% in the levetiracetam group compared with 23.3% in the placebo group ($P < 0.001$). Levetiracetam-treated patients were more likely to respond to treatment than patients receiving placebo (OR 4.77; 95% CI 2.12–10.77; $P < 0.001$). Levetiracetam-treated patients also had higher freedom rates from myoclonic seizures (25.0% versus 5.0%; $P = 0.004$) and from all seizure types (21.7% versus 1.7%; $P < 0.001$) during the 12-week evaluation period.

Another randomized, double-blind, placebo-controlled, parallel-group study enrolled adults and children (4–65 years of age)

with uncontrolled generalized tonic–clonic seizures associated with idiopathic generalized epilepsies [69]. Patients were randomized to levetiracetam (target dose 3000 mg/day for adults; 60 mg/kg/day for children) or placebo as adjunctive therapy. Among the 164 randomized patients (levetiracetam, $n = 80$; placebo, $n = 84$), the percentage who had a ≥50% reduction in the frequency of generalized tonic–clonic seizures per week (responders) during the treatment period was 72.2% for the levetiracetam group and 45.2% for the placebo group ($P < 0.001$; OR 3.28; 95% CI 1.68–6.38). During the 20-week evaluation period, seizure freedom rates were greater on levetiracetam than on placebo for both generalized tonic–clonic seizures (34.2% versus 10.7%; $P < 0.001$) and all seizure types (24.1% versus 8.3%; $P = 0.009$).

The results of these randomized studies demonstrate that levetiracetam is an effective adjunctive treatment for patients with previously uncontrolled idiopathic generalized epilepsy with myoclonic or tonic–clonic seizures, and confirm a spectrum of efficacy for levetiracetam beyond partial-onset seizures.

Suggestive evidence for levetiracetam having broad-spectrum efficacy in generalized seizure types also comes from uncontrolled studies in patients with idiopathic generalized epilepsies [70–73], including juvenile myoclonic epilepsy, eyelid myoclonia with absences [71] and other syndromes associated with absence seizures [74,75], and from studies in non-idiopathic generalized epilepsies [76–78]. In some case series, patients with progressive myoclonic epilepsy experienced dramatic improvements with the addition of levetiracetam to their regimen [77,79], and favourable responses have also been reported in children with severe myoclonic epilepsy of infancy [78]. Because of the nature of these observations, some of which are restricted to case reports, these findings require adequate confirmation in controlled studies.

Impact on patient functioning and health-related quality of life

Results from a double-blind placebo-controlled efficacy study of levetiracetam added to standard therapy in patients with partial-onset seizures [50] showed improvements over placebo in most domains of QOLIE-31 [80], a multidimensional instrument that measures the impact of epilepsy and its treatment on important dimensions of a patient's functioning and health-related quality of life (cognitive functioning, daily activities/social functioning, emotional well-being, overall quality of life, energy/fatigue, seizure worry and medication effects) [81,82]. Specifically, a beneficial impact of levetiracetam over placebo was seen for seizure worry, cognitive function, overall quality of life and total score (P-values < 0.05). Levetiracetam responders (patients with ≥50% seizure reduction) had improvements in all scores, and did better than the placebo responder group. The QOLIE-31 was further assessed in patients who enrolled into a long-term open-label follow-up study [83]. Improvements observed in levetiracetam starters ($n = 66$) were sustained long term (mean follow-up 4.1 years). Placebo starters ($n = 35$) who were converted to levetiracetam in the open-label study reached similar levels of improvement in QOLIE-31 scores to earlier starters in the long term.

In patients with idiopathic generalized epilepsy with myoclonic seizures [68], results from QOLIE-31 assessments indicated improvements in patient functioning and health-related quality of life for levetiracetam-treated patients which were larger than the limited changes reflecting stability for the placebo group (for all scores but daily activities/social functioning). Since starting study medication, more patients receiving levetiracetam than placebo reported an improvement in their overall health-related quality of life (88.3% versus 60.4%). In the study in patients with idiopathic generalized epilepsy with generalized tonic–clonic seizures [69], treatment with levetiracetam resulted in greater improvements in quality of life from the start of study than with placebo (38.3% versus 28.6% important improvement in overall quality of life, respectively), as assessed by the QOLIE-31-P scale.

Adverse effects

The adverse effect profile of levetiracetam has been well characterized during phase I, II and III clinical trials. Collective safety data from 3347 subjects receiving levetiracetam during trials, including 1422 adults and children with epilepsy, 1558 subjects evaluated in studies for other indications (cognitive disorders, anxiety and deep vein thrombosis) and 367 subjects in clinical pharmacology studies, indicated that levetiracetam is well tolerated. Safety data from several double-blinded studies reported that the overall incidence of adverse events with levetiracetam 1000 mg/day (70.8–88.8%), 2000 mg/day (75.5–83.3%) and 3000 mg/day (55–89.1%) was similar to that observed with placebo (53–88.4%) [49–52].

An analysis of withdrawal rates for adverse events has been performed on the four double-blind, placebo-controlled studies [84] and on eight open-label long-term studies [63]. In the double-blind studies overall, 106 (15.8%) of 672 patients in the levetiracetam groups withdrew from treatment, compared with 46 (13.1%) of 351 patients in the placebo groups. The overall Mantel–Haenszel OR (95% CI) for the withdrawal rate was 1.26 (0.86–1.84). Since the confidence interval encompassed unity, withdrawal rates did not differ significantly between the levetiracetam groups and the placebo groups. In the selected prospective open-label long-term studies, 14.5% (95% CI, 13.0–15.9) of patients withdrew due to treatment-emergent adverse events.

Adverse events with adjunctive therapy in adults with partial-onset seizures

Most common adverse events

The most commonly reported treatment-emergent adverse events associated with levetiracetam in randomized adjunctive therapy trials in adults with partial-onset seizures were somnolence and asthenia (>10% of patients). In a pooled analysis, somnolence was recorded in 14.8% of patients treated with levetiracetam versus 8.4% of placebo patients [85]. In the recommended dose range (1000–3000 mg/day), there was no clear dose–response relationship for adverse events [86]. For example, in one study, somnolence occurred in 20.4% of patients at 1000 mg/day levetiracetam versus 18.8% at 3000 mg/day, compared with 13.7% of placebo patients [50]. The overall incidence of asthenia was 14.7% compared with 9.1% of placebo patients, and again was not dose related. Other adverse effects included dizziness and nervousness.

Table 44.3 Overview of adverse events reported more commonly with levetiracetam administered at different dosages than with placebo in the pivotal placebo-controlled as adjunctive therapy in adults with predominantly refractory partial-onset seizures, with or without secondary generalization.

Adverse events	Incidence (% of patients)				
	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day	Levetiracetam 3000 mg/day	Levetiracetam 4000 mg/day
Betts et al. *[49]*[a]					
Somnolence	25.6		26.2		44.7
Dizziness	0		4.8		10.5
Asthenia	15.4		31		13.2
Infection	7.7		2.4		15.8
Cereghino et al. *[50]*					
Somnolence	13.7	20.4		18.8	
Dizziness	7.4	17.3		19.8	
Asthenia	11.6	16.3		12.9	
Headache	20	21.4		20.8	
Infection	12.6	27.6		26.7	
Rhinitis	8.4	13.3		6.9	
Shorvon et al. *[51]*					
Somnolence	4.5	9.4	11.3		
Dizziness	3.6	4.7	6.6		
Asthenia	8	7.5	13.2		
Headache	8.9	13.2	16		
Infection	6.3	9.4	6.6		
Ben-Menachem et al. *[52]*					
Somnolence	3.8			6.1	
Asthenia	6.7			13.8	
Headache	10.5			3.3	
Infection	3.8			7.2	

[a] Levetiracetam was started without titration of the dose.

A summary of adverse events recorded in placebo-controlled trials is given in Table 44.3. In a study where no titration was used, the incidence of somnolence, nausea and dizziness was greater during initiation of the medication and at the higher dose of 2000 mg twice daily [49]. On the other hand, a clear dose-related effect for asthenia and headache was not established. In the Cochrane review [60] based on the four double-blind, placebo-controlled studies, incidence rates for ataxia, dizziness, fatigue, nausea, somnolence, accidental injury, headache and infection were analysed. Dizziness (OR 2.36, 99% CI 1.21–4.61) and infection (OR 1.82, 99% CI 1.05–3.14) were statistically associated with levetiracetam. In contrast, accidental injury was significantly associated with placebo (OR 0.55, 99% CI 0.32 to 0.93). The incidence of ataxia, fatigue and somnolence was higher with levetiracetam than with placebo, while the incidence of headache and nausea did not differ statistically between levetiracetam and placebo. The clinical significance of infections, including upper respiratory tract (rhinitis and pharyngitis) and urinary tract infections, being increased in the levetiracetam group compared with placebo is unclear. There was no association with increases in white blood cell count, and none of the infections led to discontinuation of levetiracetam. Increased infection rates were seen in some studies and not in others, and may have been an artefact related to the terms used to report adverse effects and their coding [87].

Levetiracetam can be associated with behavioural disturbances and irritability. In premarketing studies, the category of behavioural symptoms including agitation, hostility, anxiety, apathy, emotional lability, depersonalization and depression was reported in 12.9% of levetiracetam patients compared with 6.2% of placebo patients ($P < 0.001$) [88]. Furthermore, 0.7% of levetiracetam patients reported psychotic symptoms compared with 0.2% of placebo patients, and suicidal behaviour occurred in 0.5% of levetiracetam patients versus none of the placebo patients [88]. Premarketing studies may not be ideal for assessing behavioural side-effects, because patients on antidepressants and other psychoactive medications are often excluded from clinical trials. Behavioural problems occurred at a lower rate in other populations treated with levetiracetam in early placebo-controlled trials, including patients with anxiety and cognitive disturbances [88]. This suggests that either the epileptic condition or concomitant AED use may increase the potential for behavioural problems associated with levetiracetam. Behavioural problems appear to remit when levetiracetam is discontinued. Paediatric studies have indicated that children may also be at risk for irritability and behavioural problems with levetiracetam. This is discussed below in the section on paediatric adverse effects.

In adjunctive therapy studies, the safety and tolerability of levetiracetam extended release in patients with partial-onset seizures have been similar to, if not better than, those of the immediate-release formulation. In the double-blind, placebo-controlled study conducted with the extended-release formulation, 41 (53.2%) patients randomized to levetiracetam extended release and 43 (54.4%) patients randomized to placebo reported at least one treatment-emergent adverse event. Somnolence and irritability occurred more frequently on levetiracetam extended release than on placebo [64].

Seizure aggravation

Somerville [89] explored the likelihood of seizure aggravation in randomized, placebo-controlled trials of second-generation AEDs. In the levetiracetam trials, some degree of seizure aggravation occurred in 44.8% of patients receiving placebo ($n = 310$), with ≥50% increases in seizure frequency being recorded in 15.2% and a doubling or worse in 5.8%. In the patients randomized to levetiracetam ($n = 589$), an increase in seizure frequency (25.7% for any worsening, 6.6% and 2.5% for ≥50% and ≥100% increases in seizure frequency, respectively) was significantly less likely to occur than in patients taking placebo.

In at least three of the four pivotal placebo-controlled double-blind studies of levetiracetam, exacerbation of seizures was reported among the serious adverse events that eventually led to discontinuation of the drug in a few patients. Five out of 460 epilepsy patients who received levetiracetam in these studies were reported to have had severe seizures [49,50,52]. A case series suggested that possible exacerbation of seizures may occur in a small number of patients at high doses of levetiracetam, especially in those with primary generalized epileptiform EEG discharges [90]. Others have reported that patients may worsen (increase in seizures) at higher doses of levetiracetam, and in these cases a dose reduction may lead to improvement [91]. However, in a pooled analysis, >25% worsening of seizure frequency occurred more frequently during add-on trials in the placebo groups (26%) than in the levetiracetam-treated groups (14%) [89].

Idiosyncratic reactions

Hypersensitivity and skin rash are uncommon adverse effects of levetiracetam. In placebo-controlled epilepsy trials, hypersensitivity reactions led to dose reduction or discontinuation in one patient in the levetiracetam groups, and in six in the placebo groups. There were no reports of Stevens–Johnson syndrome in the clinical trials with levetiracetam.

No clinically significant adverse effects were observed with any dosage of levetiracetam on haematology or blood chemistry tests, ECG assessments or vital signs.

No reports of serious idiosyncratic adverse effects attributable to levetiracetam are available to date. A total of 3347 patients were included in the levetiracetam safety database [92] and, as of 2007, 2 248 260 patient-years of market exposure had been estimated for levetiracetam (UCB, personal communication). Longer experience is needed to draw any conclusions about risks for rare serious idiosyncratic adverse effects, but the absence of such reports to date is reassuring.

Adverse events with monotherapy in adults with partial-onset seizures

In the monotherapy study comparing levetiracetam and controlled-release carbamazepine in newly diagnosed patients with partial epilepsy [67], discontinuation of treatment due to adverse events occurred in fewer patients on levetiracetam (14.4%) than on carbamazepine (19.2%), but the difference was not significant. Overall, there was no substantial difference in reported adverse events between the two treatment groups. However, depression and insomnia were reported significantly more often with levetiracetam, whereas back pain was experienced significantly more frequently with carbamazepine. More patients gained weight (≥7% of baseline) on carbamazepine than on levetiracetam (37/276, 13.4% versus 21/269, 7.8%).

Adverse events with the intravenous formulation

Two studies have been performed to assess the safety profile of the intravenous formulation, one in healthy subjects who received a single infusion either at high doses or at high infusion rates [93] and one in patients who received the infusion within the recommended dose range and with the recommended conditions of administration [94].

A randomized, single-blind, placebo-controlled study in 48 healthy subjects evaluated the safety, tolerability and pharmacokinetics of single doses of levetiracetam administered intravenously at higher doses (2000 mg, 3000 mg or 4000 mg over 15 min) or faster infusion rates (1500 mg, 2000 mg, 2500 mg over 5 min) than currently recommended [93]. Reported adverse events were primarily related to the central nervous system (dizziness, 52.8%; somnolence, 33.3%; fatigue, 11.1%; headache, 8.3%) and were consistent with the safety profile established for the oral formulation. Safety profiles were similar for each dose level of levetiracetam and for all infusion rates.

Among the 25 patients with epilepsy who received levetiracetam as intravenous infusions over a 4-day period [94], a total of 11 (44%) experienced at least one treatment-emergent adverse event. Overall, a 15-min infusion (500–1500 mg, twice daily) was well tolerated in patients with partial-onset seizures. Adverse events were either mild or moderate, and those most frequently reported were headache and fatigue. After the 4-day twice-daily treatment, results of clinical examination and laboratory parameters remained stable, no clinically relevant changes in vital signs or ECGs were observed, and tolerability at the injection site was very good.

The results of these studies suggest a broad tolerability margin of intravenous levetiracetam.

Adverse events with adjunctive therapy in children with partial-onset seizures

In the adjunctive therapy controlled trial performed in children with partial-onset seizures [65], the most common treatment-emergent adverse events that occurred in at least 10% of levetiracetam-treated patients and more frequently than in placebo-treated patients were somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis and nervousness (Table 44.4). The majority of these events were rated as mild to moderate in severity. The incidence of many of the common adverse events, including infection, fever, abdominal pain, nausea, diarrhoea, increased cough, rhinitis and otitis media, that were seen in both the levetiracetam and placebo groups was consistent with the expected incidence for school-age children. Psychiatric and behavioural treatment-emergent adverse events occurring in more than 5% of patients were, in decreasing order of incidence, hostility (11.9% levetiracetam, 6.2% placebo), nervousness (9.9% levetiracetam, 2.1% placebo), personality disorder (7.9% levetiracetam, 7.2% placebo), emotional lability (5.9% levetiracetam, 4.1% placebo) and agitation (5.9% levetiracetam, 1.0% placebo) [65]. The relative risk (RR) of psychiatric/behav-

Table 44.4 Incidence (%) of treatment-emergent adverse events in a double-blind, placebo-controlled adjunctive therapy trial of levetiracetam in subjects 4–16 years of age with partial-onset seizures. Only events with an incidence >5% in the levetiracetam group and greater with levetiracetam than with placebo are reported.

	Levetiracetam, % (n = 101)	Placebo, % (n = 97)
COSTART body system[a]		
Body as a whole	58.4	64.9
Digestive	36.6	38.1
Haematological and lymphatic	5.9	2.1
Metabolic and nutritional	4.0	10.3
Nervous	58.4	47.7
Respiratory	30.0	28.9
Skin and appendages	9.9	13.4
Special senses	12.9	9.3
Urogenital system	9.9	9.3
Specific adverse event		
Somnolence	23.0	11.0
Accidental injury	17.0	10.0
Vomiting	15.0	13.0
Anorexia	13.0	8.0
Rhinitis	13.0	8.0
Hostility	12.0	6.0
Cough increased	11.0	7.0
Pharyngitis	10.0	8.0
Nervousness	10.0	2.0
Asthenia	9.0	3.0
Diarrhoea	8.0	7.0
Personality disorder	8.0	7.0
Dizziness	7.0	2.0
Emotional lability	6.0	4.0
Pain	6.0	3.0
Agitation	6.0	1.0

[a] Investigator term describing each adverse event was coded to a body system and preferred term using the COSTART (*Coding Symbols for Thesaurus of Adverse Reaction Terms*) dictionary (version 5).
Reproduced with permission from ref. 65.

ioural events for children treated with levetiracetam compared with those receiving placebo was estimated for the 198 evaluable patients [95]. Patients were categorized for analysis by prior psychiatric or cognitive history, and by response status, and results were then compared with a similar analysis completed for adults treated with levetiracetam for refractory partial seizures. Although the incidence of psychiatric/behavioural events in children with partial-onset seizures treated with levetiracetam was 38.6% versus 18.6% in adults, there was also a higher incidence of psychiatric/behavioural events in children treated with placebo compared with placebo-treated adults (27.8% versus 10.5%). Therefore, the RR was similar for adults (1.77, 95% CI 1.30–2.42) and for children (1.39, 95% CI 0.93–2.08). The psychiatric adverse event profile in children with refractory partial-onset seizures is similar to that for adults, as indicated in the currently approved product labelling.

A recent randomized, double-blind, placebo-controlled adjunctive therapy study using a non-inferiority design assessed the neurocognitive effects of levetiracetam (target dose 60 mg/kg/day) in children (4–16 years of age) with partial-onset seizures [96]. Memory and attention/concentration were assessed with the Leiter International Performance Scale-Revised Attention and Memory Battery (Leiter-R AM) and the Wide Range Assessment of Memory and Learning-2 (WRAML-2). These scales were rated at baseline and after 8–12 weeks of treatment. The primary analysis was testing the non-inferiority between levetiracetam and placebo on the Leiter-R AM composite score in the per protocol population; superiority between the two groups was tested on the secondary variables. Ninety-nine patients were randomized, with 73 (46 levetiracetam, 27 placebo) in the per protocol population. Mean Leiter-R AM composite scores improved over the evaluation period in both groups. The non-inferiority of levetiracetam versus placebo was demonstrated on the Leiter-R AM in the per-protocol population, with the 90% CI lower boundary for the difference between levetiracetam and placebo on the change from baseline (–4.69) being within the pre-set non-inferiority margin of –9.0. There were no significant differences between groups in WRAML-2 scores. In the same study, the Achenbach Child Behavior Checklist (CBCL) was completed by parents or guardians to assess behavioural and emotional functioning [97]. After 12 weeks' treatment, levetiracetam did not appear to adversely affect competence in social skills, school and total competence scores (no significant difference between groups), and activities scores worsened for placebo and remained stable for levetiracetam (P = 0.0490). CBCL syndrome scores showed no statistically significant difference between groups for anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour or internalizing syndromes. However, improvement on placebo and worsening for levetiracetam was observed on aggressive behaviour (P = 0.0126), affecting broader scores of externalizing (P = 0.0114) and total problems (P = 0.0203). Most frequently reported treatment-emergent psychiatric events in the ITT population (n = 98) for levetiracetam and placebo, respectively, were aggression (12.5%, 8.8%), abnormal behaviour (7.8%, 0%), altered mood (6.3%, 0%), anxiety (6.3%, 0%) and insomnia (6.3%, 2.9%). In summary, there appeared to be no deleterious neurocognitive effects of levetiracetam used as adjunctive therapy in paediatric patients with partial-onset seizures. Behavioural findings were consistent with the overall safety profile of levetiracetam.

In the study conducted in the population aged 1 month to less than 4 years [66], there was no difference between the percentages of patients who reported treatment-emergent adverse events between the levetiracetam group (55.0%) and the placebo group (44.6%) during the 5-day treatment period. The most frequently reported treatment-emergent adverse events with a higher incidence in the levetiracetam group than in the placebo group were somnolence (levetiracetam 13.3%, placebo 1.8%) and irritability (levetiracetam 11.7%, placebo 0%).

Tolerance

There has been interest in the question of whether levetiracetam treatment is associated with the development of tolerance over time, because of a report of such an occurrence in an animal model [8]. An analysis of patients continuing on levetiracetam after the completion of controlled trials indicated that many

maintained benefits from levetiracetam therapy for up to 5 years [98]. Thirteen per cent of treated patients were seizure free for at least 6 months. A post hoc pooled analysis of three randomized placebo-controlled trials examined seizure-free days over the first 3 months of treatment and found that seizure-free days were highest in the first week of therapy (81%) and fell to 74–76% thereafter. However, after the first week, efficacy was maintained over time and was always greater than in the placebo group [62]. In an interesting case study, a patient with severe epilepsy and multiple seizures per day became initially seizure free with levetiracetam therapy, but the effect was completely lost after the first few weeks of treatment. Subsequently, she was able to regain an effect when levetiracetam was dosed only once per week, and this effect was maintained over years [99].

Teratogenicity

Levetiracetam is currently classified as a pregnancy category C drug. Few pregnancies have been reported in women treated with levetiracetam. As of November 2007, 45 pregnancies were recorded during clinical trials, of which 22 were either terminated or ended in spontaneous abortion or ectopic pregnancy. Of the 23 pregnancies ending in live births, there was one case with syndactyly, one with tetralogy of Fallot, one with heart block and one with dysplasia of the hip, all after exposure to polytherapy. The remaining 19 live births had a normal outcome. UCB Inc. established the Keppra® Pregnancy Registry in January 2005, and the expert panel that reviewed the data through August 2007 concluded that the limited amount of data available is insufficient to draw conclusions about potential risks [100].

Overdosage

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses [41].

Place in current therapy

Levetiracetam has a unique position among AEDs because of its pharmacokinetic properties, which make it easy to use, and because of its broad spectrum of activity. To summarize, levetiracetam is highly water soluble, whereas almost all other AEDs are either only partially soluble or totally insoluble, and one advantage of high water solubility is the availability of an intravenous formulation. The SV2A-related mechanism is unique. Unlike most other AEDs, levetiracetam is not significantly metabolized by cytochrome P450 enzymes. It has linear pharmacokinetics within the recommended dose range, has no potential for autoinduction, and is devoid of major drug–drug interactions inherent to most AEDs. These properties permit easy addition of levetiracetam to other drug therapies without major concerns about drug interactions. Moreover, levetiracetam is well tolerated as add-on therapy, and can be initiated at a therapeutic dose, with rapid onset of action.

Levetiracetam has been approved in Europe and in the USA as adjunctive therapy for partial-onset seizures in adults and children from 4 years of age, as adjunctive therapy for myoclonic seizures in adults and adolescents with juvenile myoclonic epilepsy from 12 years of age, and as adjunctive therapy for primary generalized tonic–clonic seizures in adults and adolescents with idiopathic generalized epilepsy from 12 years of age in Europe and from 6 years of age in the USA [68,69]. Levetiracetam demonstrated non-inferior efficacy to carbamazepine in newly diagnosed patients with partial-onset seizures [67] and it is approved for use as initial monotherapy for adults with partial-onset seizures in Europe. Despite its lack of regulatory approval for this indication in the USA, it is commonly used as monotherapy around the world and it is, in the authors' opinion, a reasonable first choice in selected patients.

Reports suggest that levetiracetam may also be effective in the management of progressive myoclonic epilepsies and other generalized epilepsy syndromes.

The introduction of an intravenous formulation has substantially increased the use of levetiracetam in hospitalized patients. Case reports have suggested its utility in status epilepticus, but this has not been proven in formal trials [101,102]. Levetiracetam is, however, ideal for use in patients hospitalized for medical conditions, due to its low potential for drug interactions and the absence of changes in laboratory safety parameters.

Overall, levetiracetam has become established as an AED with efficacy in different seizure types, and is well tolerated and easy to use. The most frequently reported adverse effects in adults with epilepsy are somnolence, asthenia, nervousness and dizziness, while in children, behavioural and cognitive problems appear to be the most commonly noted adverse events, although the relative risk for such events versus placebo is similar to that in adults. In our experience and in agreement with other reports, levetiracetam tolerability is improved by slower titration [103]. Patients and family members should be alerted to possible behavioural side-effects and encouraged to discuss these with their physician.

The recommended starting dose of levetiracetam is typically 500 mg twice daily, which is a therapeutic dose. Lately, there has been increasing preference for starting some or all patients on 250 mg twice daily, to reduce the likelihood of fatigue and irritability. Further clinical experience will determine whether this practice is beneficial. The dose can be titrated by 500–1000 mg every 1–2 weeks until maximum benefit has been obtained. In a randomized controlled study, patients were initiated on doses of 2000 mg/day or 4000 mg/day without titration [49]. Although dropout rates were not significantly different between the two dose groups and placebo, the high dose was associated with higher rates of somnolence, dizziness and nausea and responder rates did not differ between doses, indicating that, while safe, starting at 4000 mg/day is probably not beneficial. As noted above, very high doses of levetiracetam have not been proven to be more effective, and there is preliminary evidence that such doses may exacerbate seizures in some patients [91]. The seizure-suppressing effects of levetiracetam are seen relatively quickly after initiation. In a pooled analysis of clinical trial data, seizure-free days were significantly increased after the first day of therapy [62].

In children, the elimination of levetiracetam is faster than in adults and, therefore, higher doses per body weight are required. The recommended doses in children range from 20 to 60 mg/kg/

day, which are expected to produce the same plasma concentrations as in adults receiving doses between 1000 and 3000 mg/day. Initial doses in children are typically 10–20 mg/kg/day [104,105]. The characteristics of levetiracetam, particularly its low drug–drug interaction potential, make it potentially suitable for treating elderly patients, particularly those who have other illnesses and are on several other medications.

The need for laboratory monitoring is minimal when using levetiracetam. Liver function tests, electrolytes and blood counts are not expected to change in a clinically meaningful way. It would be prudent to determine serum creatinine, and to assess creatinine clearance prior to using levetiracetam when there is a possibility of renal insufficiency, or in the elderly, to determine proper dosing. Plasma levetiracetam levels are available from some laboratories, but they are likely to be useful only in selected situations.

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45 Oxcarbazepine

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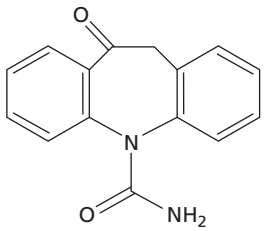

Primary indication	Adjunctive therapy or monotherapy of partial and secondary generalized seizures. Also useful to treat primary generalized tonic–clonic seizures not associated with absence and myoclonic seizures
Usual preparation	Tablets: 150, 300, 600 mg Oral suspension: 60 mg/mL
Usual dosage	Starting dosage in adults: 300 mg/day. Titration rate of 300 mg/week. Usual maintenance adult dose is 900–1800 mg/day. For children, starting dosage can be 4–5 mg/kg/day, increased by 5 mg/kg/day weekly. Usual maintenance dose in children is 20–45 mg/kg/day
Dosing frequency	Twice daily
Significant drug interactions	Enzyme-inducing antiepileptic drugs reduce the serum levels of the active metabolite monohydroxy derivative (MHD). Oxcarbazepine may increase the serum levels of phenytoin and phenobarbital, and reduces the serum levels of steroid contraceptives and felodipine
Serum level monitoring	May be useful in selected cases
Target range	3–35 mg/L
Common/important adverse effects	Dizziness, diplopia, ataxia, somnolence, headache, fatigue, rash, hyponatraemia, gastrointestinal disturbances
Main advantages	Better tolerated and fewer interactions than carbamazepine
Main disadvantages	Efficacy spectrum restricted to partial epilepsies. Higher incidence of hyponatraemia compared with carbamazepine. Interaction with oral contraceptives
Mechanism of action	Blocker of voltage-gated sodium channels and N- and P-type calcium channels
Oral bioavailability	Almost complete (in terms of MHD)
Time to peak levels	4–6 h (MHD)
Elimination	Ketoreduction to MHD, which is then cleared in urine in unchanged form and as a glucuronide conjugate
Volume of distribution	0.7–0.8 L/kg (MHD)
Elimination half-life	7–12 h (MHD)
Plasma clearance	40–50 mL/h/kg (MHD) (with higher values in patients on enzyme-inducing antiepileptic drugs and in children)
Protein binding	≤40% (MHD)
Active metabolites	MHD (monohydroxycarbazepine)
Comment	A useful antiepileptic drug for the treatment of partial and secondarily generalized seizures, with some advantages over carbamazepine

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Introduction

Carbamazepine and oxcarbazepine were synthesized at the J. R. Geigy AG Laboratories, Basle, Switzerland, in 1957 and 1963 respectively, based on structural similarities to tricyclic antidepressants. Although similar in their primary mechanism of antiseizure action, carbamazepine and oxcarbazepine differ in secondary mechanisms of action, metabolic pathways and propensity for drug interactions, and are therefore not interchangeable in therapeutic use [1].

Clinical trials of oxcarbazepine as an antiepileptic agent began in 1977, and the drug was introduced commercially in Denmark in 1990. Oxcarbazepine has been available throughout the European Union since 1999 and in the USA since 2000. In most countries it is approved for use as monotherapy or add-on treatment of partial seizures with or without secondary generalization for adults and children aged 4 and above [2].

Chemistry

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz[*b*,*f*]azepine-5-carboxamide) is a 10-keto analogue of carbamazepine [2]. It is a highly lipophilic compound with very low water solubility [2]. Oxcarbazepine is rapidly reduced to its 10-monohydroxy derivative (Fig. 45.1), also known as MHD (10,11-dihydro-10-hydroxy-5H-dibenz[*b*,*f*]azepine-5-carboxamide), which is found in serum as a mixture of its enantiomers *R*-(–)-MHD (20%) and *S*-(+)-MHD (80%) [3].

Both oxcarbazepine and MHD are pharmacologically active. However, in humans, oxcarbazepine is almost completely metabolized to MHD [2,3], which is found in serum at concentrations several-fold higher of those of the parent drug and is therefore primarily responsible for the pharmacological effect. MHD has greater water solubility, but no parenteral preparation of either oxcarbazepine or MHD is currently available.

Pharmacology

Carbamazepine, oxcarbazepine and MHD exhibit similar activity in standard animal seizure models. In the maximal electroshock test, which predicts efficacy against partial-onset and generalized tonic–clonic seizures, carbamazepine, phenytoin, oxcarbazepine and MHD were equally potent [2,4]. Carbamazepine, oxcarbazepine and MHD lacked efficacy in seizure models predictive of efficacy against absence seizures (strychnine, pentylenetetrazole and picrotoxin) [2,4].

Oxcarbazepine and MHD modulate voltage-sensitive cationic channels [4]. The mechanism of blockade of sodium channels is similar to that of phenytoin and carbamazepine, but MHD has a greater affinity for the inactivated state of the channel [4]. MHD inhibits N- and P-type calcium channel currents, unlike carbamazepine, which has a greater effect on L-type channels [4]. Elevation of hippocampal dopamine and serotonin levels has also been reported [5].

Pharmacokinetics

Steady-state serum concentrations of MHD are reached in 2–3 days of twice-daily dosing; they are ninefold higher than those of

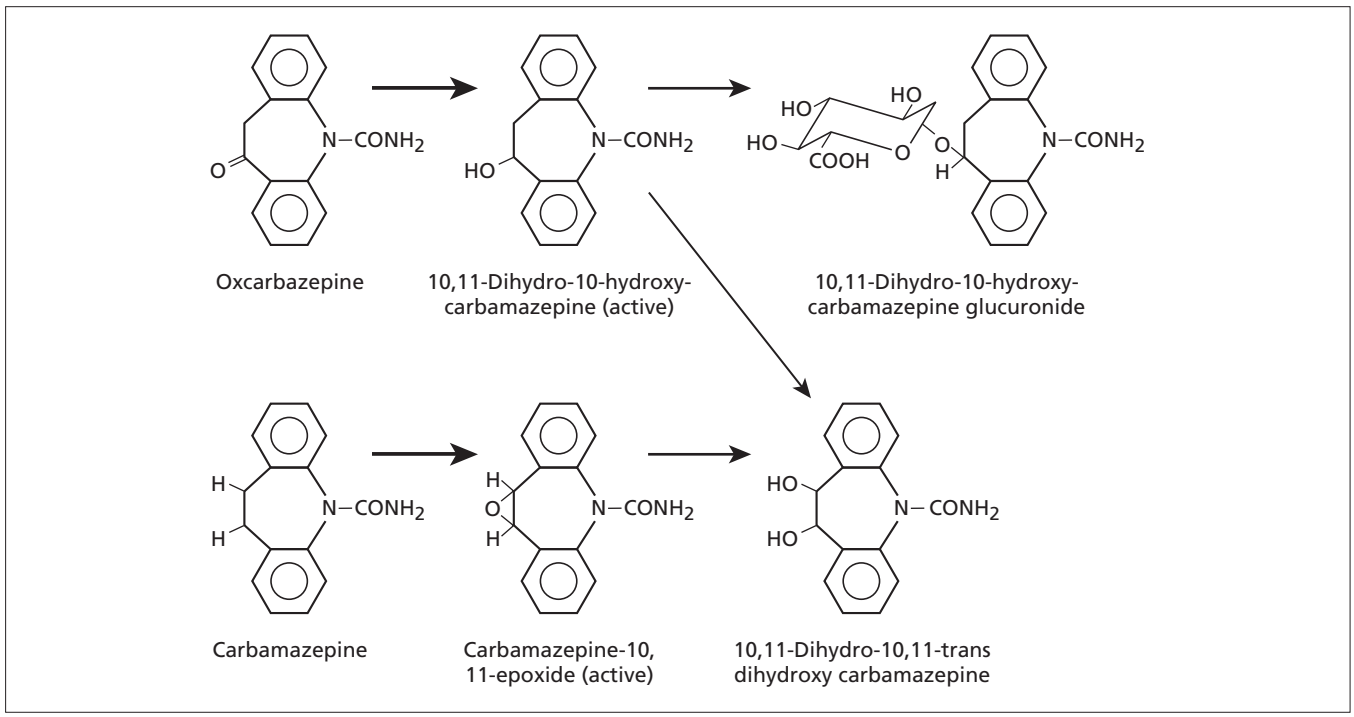

Fig. 45.1 Metabolism of oxcarbazepine and carbamazepine. From refs 10 and 15 with permission.

oxcarbazepine. The dose–concentration relationship is linear across a wide dose range (300–2400 mg/day) [2]. The following relationship between MHD concentration and dose of oxcarbazepine has been described, over the range 300–2700 mg/day [6]:

MHD concentration (mg/L) = 0.93 × oxcarbazepine dose (mg/kg)

Absorption

Oxcarbazepine is rapidly and completely absorbed (>95%). Although its peak concentrations are achieved within 1 h, they are very low because the drug is rapidly reduced to the active 10-monohydroxy derivative (MHD), which reaches peak concentrations in 4–6 h [3]. Oral bioavailability is not significantly affected by food intake, and therefore oxcarbazepine can be given with or without food [2].

Distribution

The volume of distribution of oxcarbazepine is 0.3 L/kg and that of MHD is 0.7–0.8 L/kg, or about 49 L [2], indicating distribution in total body water. As a lipophilic substance, MHD is widely distributed in the body and easily passes the blood–brain barrier. Both oxcarbazepine and MHD exhibit low protein binding (33–38% for MHD and 60–67% for oxcarbazepine), independent of the dose [7]. Therefore, oxcarbazepine does not produce protein-binding interactions with highly protein-bound drugs such as phenytoin and valproic acid.

Biotransformation and elimination

Oxcarbazepine is rapidly eliminated from plasma, and therefore its half-life (1–2.5 h) is of no practical significance. The half-life of MHD is 9.3 ± 1.8 h [2,8]. The elimination is monoexponential and follows linear kinetics in patients with epilepsy on oxcarbazepine monotherapy or polytherapy. Unlike carbamazepine, no autoinduction during early therapy occurs [8].

The metabolic pathways of carbamazepine and oxcarbazepine differ significantly (see Fig. 45.1). Carbamazepine is metabolized by cytochrome P450 (CYP) oxidases with an arene oxide (epoxide) intermediate [8]. Oxcarbazepine is rapidly and extensively metabolized by cytosolic aldo-ketoreductase enzymes in the liver to the active metabolite 10,11-dihydro-10-hydroxycarbamazepine or monohydroxycarbazepine (MHD, 96%). Aldo-ketoreductases are practically non-inducible enzymes. A small fraction of oxcarbazepine (4%) is oxidized to an inactive dihydroxy derivative (DHD). MHD is partly glucuronidated by microsomal uridine-diphosphoglucuronyltransferases (UGTs).

Most of an orally administered oxcarbazepine dose is accounted for in urine as MHD glucuronide (51%) and unchanged MHD (28%). The dihydroxy derivative accounts for 3% of the dose excreted in the urine, with <13% of the drug excreted as minor conjugates of oxcarbazepine and MHD [8].

Pharmacokinetics in special groups

Steady-state MHD concentrations, adjusted for body weight, in older children and adolescents were comparable to those in adults, but areas under the concentration–time curve (AUC) for MHD were 30% lower in children under 8 years of age [9]. Higher mg/kg doses may therefore be required in young children [2]. AUC values for MHD were significantly higher in elderly patients (>60 years of age), suggesting that dosing should be lower in this group. This may be explained by age-related decreases in creatinine clearance [10].

Serum MHD levels have been reported to drop by 28–36% [11] or even more [12] during pregnancy, and to return to baseline values shortly after delivery.

Mild to moderate hepatic dysfunction did not alter the pharmacokinetics of oxcarbazepine or MHD, but the pharmacokinetics of oxcarbazepine has not been evaluated in severe hepatic dysfunction [2,8].

Elimination is little affected by mild to moderate renal dysfunction, but patients with creatinine clearances of <30 mL/min/1.73 m^2 exhibited significant increases in elimination half-life and plasma concentrations of MHD [6].

Drug interactions

In vitro studies indicate that both oxcarbazepine and MHD are competitive inhibitors of cytochrome CYP2C19. High doses of oxcarbazepine may produce clinically significant inhibition of CYP2C19, with consequent elevations of serum concentrations of substrates such as phenobarbital and phenytoin [2,13].

Interactions between antiepileptic drugs (AEDs) and oxcarbazepine are listed in Table 45.1. The addition of oxcarbazepine to existing AED regimens produces increases in serum phenytoin, phenobarbital and carbamazepine-10,11-epoxide concentrations and a decrease in carbamazepine concentrations. When enzyme-inducing AEDs are added to oxcarbazepine, plasma MHD concentrations decrease by 29–40%, which may require an increase in oxcarbazepine dose.

Oxcarbazepine has a weaker enzyme-inducing activity than carbamazepine on CYP enzymes [14]. However, breakthrough bleeding and loss of contraceptive efficacy may occur when oxcarbazepine is added to a stable regimen of oral contraceptives, due to increased metabolism of ethinylestradiol and levonorgestrel [15,16]. Oxcarbazepine may reduce serum felodipine levels, but to a much lesser extent compared with the decrease in serum felodipine levels caused by carbamazepine [14]. A single case report suggested that oxcarbazepine may also reduce ciclosporin

Table 45.1 Summary of interactions between antiepileptic drugs (AEDs) and oxcarbazepine.

Influence of AED on	Influence of oxcarbazepine on	
	AED concentration	MHD concentration
Phenytoin	0–40% increase	29–35% decrease
Phenobarbital	14–15% increase	30–31% decrease
Valproic acid	No influence	0–18% decrease
Carbamazepine	0–22% decrease	40% decrease
Carbamazepine-10,11-epoxide	30% increase	Not studied
Clobazam	Not studied	No influence
Felbamate	Not studied	Not studied
Lamotrigine	No influence or modest decrease	No influence

A levels, but more data are required to confirm this interaction [17]. Unlike carbamazepine, oxcarbazepine does not interact significantly with warfarin, cimetidine, propoxyphene or erythromycin [18].

Because of their differing effects on the CYP enzyme systems, substitution of oxcarbazepine for carbamazepine may result in de-induction and a consequent increase in the serum concentration of inducible concomitant AEDs, such as lamotrigine, valproic acid, topiramate and zonisamide [19].

Serum level monitoring

Since oxcarbazepine is rapidly converted to MHD *in vivo*, only measurement of MHD, usually by high-performance liquid chromatography, is useful. In a group of 214 patients treated with a clinically optimized dose, the mean plasma level of MHD was 15.3 mg/L, but with a wide individual variation between patients [20]. A range of therapeutic concentrations of 3–35 mg/L has been suggested, although variability in response at these concentrations is considerable [17]. Routine monitoring of serum levels is generally not recommended, though it may be helpful to assess compliance, or to gauge dosage in the presence of enzyme-inducing concomitant AEDs. Since MHD levels have been reported to drop by 28–36% during pregnancy [11,12], it is probably worthwhile monitoring MHD levels during pregnancy and in the postpartum period.

Efficacy

The efficacy of oxcarbazepine has been established in many randomized, controlled clinical trials. Oxcarbazepine was compared with carbamazepine [19,21,22], phenytoin [23,24], valproate [25] and levetiracetam [26] in controlled monotherapy trials. Other randomized trials utilized oxcarbazepine monotherapy in comparison with either placebo [27,28] or lower-dose oxcarbazepine [29,30]. Randomized controlled trials of adjunctive therapy for refractory patients have enrolled adults aged 15–65 [31], children aged 3–17 years [32], and infants from 1 month to 4 years of age [33].

All of these trials were designed to evaluate patients with partial-onset seizures with or without secondary generalization, although in some trials patients with primary generalized tonic–clonic seizures were also included. Oxcarbazepine is not indicated for absence, myoclonic and other types of generalized seizures other than tonic–clonic seizures, and indeed may exacerbate them [34].

Efficacy in comparison with carbamazepine

Three controlled trials compared oxcarbazepine with carbamazepine (Table 45.2). In a randomized, double-blind cross-over study, 48 patients taking carbamazepine along with other AEDs had their carbamazepine replaced by oxcarbazepine [21]. Patients took oxcarbazepine and carbamazepine for 12 weeks each, in addition to the titration period. Oxcarbazepine significantly reduced tonic–clonic and tonic seizures in comparison with carbamazepine, but there was no differential effect on complex partial seizures. The possible increases in serum concentration of inducible AEDs during the oxcarbazepine intervals complicates interpretation of these results. Patients taking phenytoin monotherapy were converted to either oxcarbazepine or carbamazepine in another double-blind trial, and no efficacy differences were found [19]. In a trial enrolling 235 patients with newly diagnosed epilepsy [22], patients with previously untreated primary generalized tonic–clonic seizures or partial seizures with or without secondary generalization were begun on either oxcarbazepine 300 mg/day or carbamazepine 200 mg/day with dosage adjustments during a 4–8-week titration period. At the end of the 48-week maintenance phase, carbamazepine patients were taking a mean dose of 685 mg/day, while oxcarbazepine patients were taking 1040 mg/day. Fifty-two per cent of oxcarbazepine patients and 60% of carbamazepine patients were seizure free during this year-long study, not a significant difference.

Oxcarbazepine is equal in efficacy to carbamazepine in head-to-head comparisons. However, it is more effective in certain patients, based on data from monotherapy trials in which some patients were converted from carbamazepine to oxcarbazepine,

Table 45.2 Randomized clinical trials comparing oxcarbazepine with carbamazepine.

Study	Number and type of patients	Trial design	Mean dose per day	Efficacy results	Percentage of dropouts for adverse events
Houtkooper *et al*. [21]	48 adult inpatients on carbamazepine plus one to three drugs	Crossover	Oxcarbazepine: 2628 mg Carbamazepine: 1302 mg	9% seizure reduction on oxcarbazepine (NS)	None on either treatment
Reinikainen *et al*. [19]	40 adults unsatisfactorily treated with phenytoin	Conversion to oxcarbazepine or carbamazepine, parallel group	Oxcarbazepine: 13.1 mg/kg Carbamazepine: 8.3 mg/kg	No difference	None on either treatment
Dam *et al*. [22]	149 adults newly diagnosed with partial or generalized tonic–clonic seizures	Parallel group	Oxcarbazepine: 1040 mg Carbamazepine: 684 mg	Oxcarbazepine: 52% seizure free Carbamazepine: 60% seizure free (NS)	Oxcarbazepine: 14% Carbamazepine: 25% ($P = 0.04$)

NS, not statistically significant.

Table 45.3 Randomized clinical trials comparing oxcarbazepine with phenytoin or valproate. All studies used a parallel group-design.

Study	Number and type of patients	Mean dose per day	Efficacy results (% seizure free)	Percentage of dropouts for adverse events
Bill *et al*. [23]	287 adults with newly diagnosed partial or generalized tonic–clonic seizures	Oxcarbazepine 1028 mg Phenytoin 313 mg	Oxcarbazepine: 59 Phenytoin: 58 (NS)	Oxcarbazepine: 3 Phenytoin: 1 ($P = 0.002$)
Guerreiro *et al*. [24]	193 children (5–18 years) with newly diagnosed partial or generalized tonic–clonic seizures	Oxcarbazepine 672 mg (18.8 mg/kg) Phenytoin 226 mg (5.8 mg/kg)	Oxcarbazepine: 61 Phenytoin: 60 (NS)	Oxcarbazepine: 2.5 Phenytoin: 18 ($P = 0.002$)
Christe *et al*. [25]	249 adults with newly diagnosed partial or generalized tonic–clonic seizures	Oxcarbazepine 1053 mg Valproate 1146 mg	Oxcarbazepine: 57 Valproate: 54 (NS)	Oxcarbazepine: 12 Valproate: 58 (NS)

NS, not statistically significant.

and from open-label experience. Since there are no systematic data on conversion from oxcarbazepine to carbamazepine, the converse may or may not be true.

Efficacy in comparison with other antiepileptic drugs

In patients with newly diagnosed epilepsy, the efficacy of oxcarbazepine is equivalent to that of phenytoin and valproate (Table 45.3). Fifty-nine per cent of patients with a new diagnosis of partial seizures with or without secondary generalized seizures, or generalized tonic–clonic seizures without partial onset, were seizure free while taking oxcarbazepine during a 48-month maintenance treatment period, compared with 58% receiving phenytoin [23]. The mean daily dose at the start of the maintenance period was 1028 mg for oxcarbazepine and 313 mg for phenytoin. A similar result emerged from a study of 193 children aged 5–18 years, who were randomized to oxcarbazepine or phenytoin after a new diagnosis of epilepsy [24]. Sixty per cent of each group was seizure free during the maintenance period. However, in both these studies oxcarbazepine was better tolerated, and phenytoin therapy was more likely to fail because of adverse effects. A study of similar design compared oxcarbazepine with valproate among 249 patients aged 15–65 years [25]. Seizure-free rates were 57% for oxcarbazepine and 54% for valproate, not significantly different. The median daily maintenance dose was 900 mg for each drug.

In a large, randomized, unblinded study (the SANAD trial), oxcarbazepine was compared with carbamazepine, lamotrigine, gabapentin and topiramate for treatment of newly diagnosed partial epilepsy [35]. No significant differences in efficacy between oxcarbazepine and the other drugs emerged, although fewer patients took oxcarbazepine than the other drugs because it was added as a treatment arm later.

Oxcarbazepine was slightly less effective (72% seizure free) than levetiracetam (90% seizure free) in a randomized, open-label trial of 39 children with benign epilepsy with centrotemporal spikes, though the difference was not statistically significant [26].

Monotherapy in refractory patients

The studies demonstrating monotherapy efficacy in newly diagnosed patients [22–25] led to the design of studies to evaluate monotherapy efficacy in patients with refractory partial-onset seizures. All of them led to statistically significant differences in favour of oxcarbazepine, or in favour of high-dose rather than low-dose oxcarbazepine.

Patients removed from therapy for presurgical video-EEG monitoring ($n = 102$) were randomized to resume therapy with either oxcarbazepine 2400 mg/day or placebo while remaining in hospital [27]. Patients exited the trial after completing 10 days of treatment, or after meeting exit criteria suggesting drug failure, such as four partial-onset seizures within this period. Forty-seven per cent in the oxcarbazepine arm and 84% in the placebo arm met one of the exit criteria. This study also demonstrated the feasibility of quick initiation of oxcarbazepine when necessary for inpatients: 1500 mg on the first day, then 2400 mg on subsequent days.

Two outpatient studies have employed a more gradual conversion to oxcarbazepine monotherapy for patients with refractory partial-onset seizures [29,30]. Outpatients aged 12 years or older were converted from one or two baseline AEDs over 14 days to monotherapy with oxcarbazepine 300 mg/day or 2400 mg/day [29]. Patients exited if there was a twofold increase in partial seizure frequency over baseline during any 2-day or 28-day period, if a single tonic–clonic seizure occurred if none had occurred previously in the past 6 months, or if judged necessary by the investigator. During the 112-day maintenance period, 41% of the high-dose group met one of the exit criteria compared with 93% of the low-dose group. The second study used a similar design, but all patients were stabilized on carbamazepine monotherapy before conversion to oxcarbazepine 300 or 2400 mg/day as monotherapy [30]. Fifty-nine per cent of the oxcarbazepine 2400 mg/day group and 89% of the oxcarbazepine 300 mg/day group met one of the exit criteria.

A true placebo control was used in another study of newly diagnosed patients with currently untreated partial seizures, who received a placebo or 1200 mg oxcarbazepine per day during the 90-day double-blind treatment phase [28]. The primary endpoint, median time to the first seizure, was 11.7 days in the oxcarbazepine group and 3.2 days in the placebo group.

Adjunctive therapy versus placebo (or low-dose oxcarbazepine)

Randomized controlled trials in which oxcarbazepine or placebo was added to existing therapy for patients with inadequately

Table 45.4 Randomized clinical trials of adjunctive oxcarbazepine therapy. All studies used a parallel group-design.

Study	Number and type of patients	Mean percentage reduction in seizure frequency (versus baseline)	Percentage of dropouts for adverse events
Barcs *et al*. [31]	694 adults with refractory partial-onset seizures	Placebo: 8 Oxcarbazepine 600 mg: 26 Oxcarbazepine 1200 mg: 40 Oxcarbazepine 2400 mg: 50 ($P = 0.001$, all doses versus placebo)	Placebo: 9 Oxcarbazepine 600 mg: 12 Oxcarbazepine 1200 mg: 36 Oxcarbazepine 2400 mg: 67
Glauser *et al*. [32]	267 children (3–17 years) with refractory partial-onset seizures	Placebo: 9 Oxcarbazepine 30–46 mg/kg: 35 ($P = 0.0001$) (median percentage reduction in seizure frequency)	Placebo: 3 Oxcarbazepine: 10
Pina-Garza *et al*. [33]	128 infants/children (1 month to 4 years) with refractory partial-onset seizures	Oxcarbazepine 10 mg/kg: 46 Oxcarbazepine 60 mg/kg: 83 ($P = 0.05$) (median percentage reduction in seizure frequency of electrographic seizures with a behavioural correlate per 24 h, assessed with a 72-h video-EEG recording)	Oxcarbazepine 10 mg/kg: 2 Oxcarbazepine 60 mg/kg: 3

controlled partial-onset seizures are listed in Table 45.4. The results of all these studies demonstrated statistically significant reductions in seizures for oxcarbazepine over placebo or for high-dose over low-dose oxcarbazepine.

A dose-ranging trial enrolled 694 patients aged 15–65 years in a parallel comparison of placebo and three doses of oxcarbazepine [31]. A linear dose–response association was found, with median percentage reductions of 8%, 26%, 40% and 50% for placebo and 600, 1200 and 2400 mg/day oxcarbazepine respectively. However, discontinuation rates for adverse events also increased with increasing dosage, with 66.7% of patients discontinuing treatment in the highest dose group. Among the 75% of patients who were taking carbamazepine as one of their baseline drugs, the improvement in seizure frequency after adding oxcarbazepine was virtually identical to that achieved in the entire study group. Although the patients in this study taking carbamazepine were presumably being treated with an optimal dose, the results do not fully answer the question of whether the addition of oxcarbazepine to carbamazepine produces a qualitatively different effect on seizure frequency or merely an additive one, i.e. whether the same effect could have been achieved by simply adding more carbamazepine.

In another adjunctive therapy study, children aged 3–17 years with inadequately controlled partial-onset seizures taking one or two baseline drugs were assigned to oxcarbazepine 30–46 mg/kg/day or to placebo for a 112-day double-blind treatment phase, after a 56-day baseline [32]. The primary endpoint, percentage change in seizure frequency from baseline, was 35% for oxcarbazepine and 9% for placebo.

Infants and young children aged 1 month to <4 years with uncontrolled seizures were randomized to have either oxcarbazepine 10 mg/kg or 60 mg/kg per day added to one or two baseline drugs [33]. Seizures confirmed by both clinical and EEG evidence were reduced 46% by the low dose and 83% by the high dose.

Other studies in epilepsy

Oxcarbazepine was reported to be effective in the treatment of eight children with nocturnal frontal lobe epilepsy [36].

A quality of life measure (QOLIE-31) improved significantly when patients were converted to oxcarbazepine monotherapy from any of three previous monotherapies: carbamazepine ($n = 121$), phenytoin ($n = 65$) or valproate ($n = 45$) [37]. Results from several open-label patient series suggest that retention on oxcarbazepine therapy is relatively high. For example, in a group of 175 patients, after 1 year 91% of those on initial oxcarbazepine monotherapy and 71% of those converted to oxcarbazepine as their second monotherapy continued to take the drug [38]. It is difficult to define tolerance to antiepileptic efficacy, but these large experiences suggest that tolerance to oxcarbazepine is not a greater problem than with other AEDs.

Non-epilepsy indications

Oxcarbazepine has been used to treat neuropathic pain [39] and there have been some reports suggestive of efficacy in acute mania and, as add-on use, in acute bipolar depression and bipolar depression prophylaxis. A randomized controlled trial, however, demonstrated no benefit over placebo for bipolar affective disorders in children and adolescents [40].

Adverse effects

Central nervous system effects

The most common adverse effects seen early in treatment and those which most often lead to oxcarbazepine discontinuation affect the central nervous system (CNS) (Table 45.5). Adverse effect rates are best assessed in comparison with placebo in monotherapy studies. In these studies, the most common CNS side-effects were headache, somnolence and dizziness [1]. Ataxia, fatigue and diplopia or visual blurring were uncommon during monotherapy, though present much more often than with placebo in adjunctive therapy trials. This adverse effect profile is qualitatively similar to that seen with carbamazepine.

In the oxcarbazepine monotherapy trials, the rate of adverse effects judged as 'severe' by the investigators did not differ from

Table 45.5 Percentage of patients experiencing the five most common central nervous system adverse effects in oxcarbazepine trials.

Adverse effect	Initial monotherapy trials		Adjunctive trials[a]	
	Oxcarbazepine (n = 440)	Placebo (n = 66)	Oxcarbazepine (n = 705)	Placebo (n = 302)
Headache	37	12	26	21
Somnolence	22	6	26	12
Dizziness	20	4	30	11
Ataxia	2	0	17	5
Diplopia	0.5	0	24	3

[a] Combined adult [31] and paediatric [32] data.

placebo, valproate, phenytoin and carbamazepine, ranging from 5.8% to 8.2% [22–25]. In these direct comparative trials, discontinuation rates were significantly lower for oxcarbazepine in comparison with carbamazepine (14% versus 26%) [22] and phenytoin [23,24], but not in comparison with valproate [25]. Discontinuation rates are, as expected, higher in adjunctive therapy trials, mostly because of adverse effects. Among adults, 9% of patients taking placebo and concomitant medications stopped treatment because of adverse effects, in comparison with 12%, 36% and 67% for patients taking oxcarbazepine 600, 1200 and 2400 mg/day, respectively [31]. In an adjunctive study in children [32], there was a 10% dropout rate in the oxcarbazepine treatment group, versus 3% in the placebo group. These clinical trials employed rather rapid titration rates. Dropout rates due to adverse effects may be lower with more gradual introduction.

Except for early, dose initiation CNS effects such as somnolence, cognitive effects appear to be relatively benign. Small studies have reported no difference in cognitive function tests between oxcarbazepine and phenytoin [41], and before and 4 months after initiation of oxcarbazepine [42]. In an open-label, 6-month trial enrolling 112 children randomized to oxcarbazepine, carbamazepine or valproate, none of the three drugs adversely affected the results of cognitive function tests [43].

Gastrointestinal effects

The incidence of nausea was higher than with placebo only during adjunctive oxcarbazepine therapy: 22.5% for all oxcarbazepine doses compared with 8.1% for placebo [31]. Nausea was the most common reason for dropout among children in an adjunctive therapy study [32]. Among infants aged 4 months to <4 years, gastrointestinal effects and somnolence were the two most common side-effects of adjunctive oxcarbazepine, and were much more common at the high dose (60 mg/kg/day) than at the low dose (10 mg/kg/day).

Rash

Oxcarbazepine is less likely to cause a skin rash than carbamazepine. 'Allergy' resulted in medication withdrawal in 10% of oxcarbazepine-treated and 16% of carbamazepine-treated patients in a comparative study [22]. Data from all clinical trials suggest that there is a 3% incidence of rash with oxcarbazepine compared with 7% with carbamazepine [2]. Cross-reactivity with carbamazepine has been reported, with 25.5% of patients who had a history of skin rashes on carbamazepine also developing a rash when they were converted to oxcarbazepine [44]. A few cases of Stevens–Johnson syndrome have been reported [2,45].

Hyponatraemia

The only side-effect of oxcarbazepine which is clearly more common than with carbamazepine is hyponatraemia. This is usually asymptomatic, but could cause an increase in seizures and other adverse effects when serum levels fall below 125 mEq/L. Among 97 oxcarbazepine-treated patients, the incidence of sodium <134 mEq/L was 29.9% compared with 13.5% among 451 carbamazepine-treated patients [46]. The incidence of hyponatraemia varies directly with age, with sodium levels below 135 mEq/l occurring at least once in 0.2% of children, 3.6% of adults aged 17–64 years and 7.3% of those 65 years or older in a database maintained by the manufacturer [47]. Patients prone to hyponatraemia for other reasons, such as those taking natriuretic diuretics, may be at higher risk. The fall in serum sodium usually occurs within the first 3 months of therapy, but may happen later if the dose is increased [48]. Hyponatraemia due to oxcarbazepine was unrelated to altered antidiuretic hormone (ADH) levels in one study, but may have been caused by increased renal tubular sensitivity to ADH [47].

Bone and other systems

Long-term effects on bone health are unknown. In a single study, both carbamazepine and oxcarbazepine reduced serum vitamin D levels [49]. The authors suggest that these drugs may produce a secondary hypoparathyroidism and that patients may need surveillance of bone density or replacement therapy. No significant adverse effects on liver, blood, pancreas or other organs have been reported thus far [2].

Special populations

Types and rates of adverse effects among children [24,32], and among patients with intellectual disability [50], are generally similar to those seen in adult populations. Although hyponatraemia is more common in the elderly [47], discontinuation rates due to adverse effects among elderly adults are the same as among younger adults [51]. The most common adverse effects among 52 patients aged 65 or older were vomiting (19%), dizziness (17%), nausea (17%) and somnolence (15%) [51].

Teratogenicity

When given to pregnant rats in intermediate and high doses, oxcarbazepine was associated with an increased incidence of craniofacial, skeletal and cardiovascular malformations, decreased fetal body weights and increased rates of fetal death [2]. In a retrospective database review, six congenital malformations occurred among 248 infants born to women who had received oxcarbazepine monotherapy during pregnancy (2.4%), suggesting that it is relatively safe in comparison with other AEDs [52]. However, there are no well-controlled studies of oxcarbazepine in pregnant women, and the drug should be used only if the benefits outweigh the risk to the fetus (Food and Drug Administration pregnancy category C) [2].

Current place in therapy

Oxcarbazepine is an effective drug for the treatment of partial-onset seizures and for primary or secondary generalized tonic–clonic seizures, when used as either monotherapy or adjunctive therapy. Its efficacy in the monotherapy of newly diagnosed patients is comparable to that of carbamazepine, phenytoin and valproate, but it is often better tolerated than carbamazepine and phenytoin. Its efficacy as adjunctive therapy for refractory partial-onset seizures is comparable to that of the other AEDs tested in controlled studies of similar design, although meta-analytical comparisons between different clinical trials are scientifically tenuous. Oxcarbazepine tolerability as an adjunctive drug is good for children treated with 30–46 mg/kg/day [40] and for adults treated with 600–1200 mg/day, but tolerability is considerably worse for adults treated with 1800–2400 mg/day [39]. As carbamazepine and oxcarbazepine side-effects are often similar and additive, the tolerability of oxcarbazepine as an adjunct to carbamazepine is likely to be much better in clinical practice if concomitant carbamazepine dosage is reduced as oxcarbazepine is added.

Dose initiation

The manufacturer recommends beginning oxcarbazepine at 600 mg/day in two divided doses, with increases of 600 mg/day at weekly intervals to a recommended daily dose of 1200 mg [1]. Clinical experience suggests, however, that for most outpatients a slower titration schedule is better tolerated. An advisory board of UK physicians has recommended oxcarbazepine monotherapy initiation at 300 mg/day, beginning with 150 mg at bedtime on the first day and then 150 mg twice daily thereafter [53]. Other authorities also suggest beginning with lower doses, such as 300 mg/day in two divided doses, or even 150 mg/day with increases of 150 mg/day every 2 days [54]. A simple schedule which can be used for most adults for monotherapy initiation, adjunctive therapy or substitution for carbamazepine is oxcarbazepine 300 mg at bedtime for 1 week, with weekly increases of 300 mg/day, adhering to a twice-daily schedule.

Oxcarbazepine can be titrated more quickly when this is desirable, and rather rapidly if necessary. There were surprisingly few dropouts because of side-effects (only 3 of 51) in the inpatient trial in which a 2400-mg dose was reached on the second day of treatment [27]. Outpatients needing rapid attainment of an effective dose can be started at 600 mg/day in two divided doses, and inpatients can be started at 900–1200 mg/day in two or three divided doses. Oxcarbazepine has been used successfully for inpatient prophylaxis of early postoperative seizures in brain tumour patients without problematic hyponatraemia [55].

For children aged 4–16 years, the recommended starting dose is 8–10 mg/kg/day [1], but 4–5 mg/kg/day, not over 300 mg/day, may be better tolerated, adhering to a twice-daily schedule. Weekly increases of about 5 mg/kg/day are appropriate.

Conversion from carbamazepine

Conversion from carbamazepine to oxcarbazepine may be considered for patients who have dose-limiting side-effects of carbamazepine, or problems with drug interactions. For example, it is often difficult to achieve adequate serum valproic acid concentrations in patients taking carbamazepine. Overnight conversion is usually well tolerated [56], especially for patients taking carbamazepine doses of 800 mg/day or less [51], but many physicians favour a more gradual approach. A conversion ratio of carbamazepine to oxcarbazepine of 1 : 1.5 is reasonable for initial carbamazepine doses of 800 mg/day or less, but a ratio of 1 : 1 or 1 : 1.25 is often better tolerated for higher initial carbamazepine doses.

Maintenance treatment

For adults with new-onset epilepsy, oxcarbazepine daily dosages of 900–1200 mg/day have been shown to be effective and well tolerated [22,23,25]. For smaller adults and the elderly, 900 mg/day is a good target for initial therapy.

A reasonable dose for children, based on a childhood new-onset monotherapy study [24], is 20 mg/kg/day. If no significant reduction in seizures is achieved, even without clinical toxicity, at 1800 mg/day in adults or 45 mg/kg/day in children, then further increases are unlikely to be very productive.

The elimination half-life of MHD (about 10 h) suggests that three daily doses would be optimal, but most of the clinical trials utilized two daily doses. No difference in efficacy nor in incidence of adverse effects was found in a study comparing twice-daily with three times daily dosing [54]. An occasional patient may tolerate three daily doses better than two because of fewer peak-dose side-effects.

Monitoring of serum sodium

The manufacturer states that measurement of serum sodium levels should be considered, particularly for susceptible patients (e.g. those taking diuretics), or if symptoms possibly indicating hyponatraemia develop, such as nausea, malaise, headache, lethargy, confusion or obtundation [2]. Assessment of serum sodium at baseline, after 1–2 months of therapy, and after large dose increases, will detect most significant drops in serum sodium, although this procedure is not mandatory. Elderly patients are more susceptible, children less [47].

Withdrawal

As with all AEDs, it is prudent to withdraw oxcarbazepine gradually. Patients withdrawn from oxcarbazepine for seizure monitoring were more likely to have generalized tonic–clonic seizures by the second day than those withdrawn from phenytoin; the authors of this paper suggested that a rebound phenomenon may exist [57].

Advantages and disadvantages of oxcarbazepine

The efficacy of oxcarbazepine for partial-onset and generalized tonic–clonic seizures, as both monotherapy and adjunctive therapy, has been thoroughly established by the results of many well-controlled studies involving all ages of patients. During nearly 20 years of clinical use, there has been a remarkably good safety record, with few dangerous side-effects. The rate for both minor and serious skin rashes is low, and definitely lower than for carbamazepine. Drug interactions are fewer than with most older generation AEDs, including carbamazepine.

However, there is no clear population advantage in efficacy for oxcarbazepine over carbamazepine or other first-line drugs;

oxcarbazepine is more expensive than older AEDs in most countries, and it is more likely than carbamazepine to produce hyponatraemia. It is not effective for, and may exacerbate, absence and myoclonic seizures. It is not completely free of drug interactions, and can reduce the efficacy of birth control pills. Safety for use during pregnancy has not been established conclusively, and pregnancy may reduce oxcarbazepine serum levels.

On balance, oxcarbazepine is a useful first-line agent suitable for partial-onset seizures in children and adults, and is better tolerated than carbamazepine and phenytoin for most patients. It compares favourably in terms of efficacy, safety and tolerability with other newer drugs for epilepsy, although few well-controlled comparisons among newer agents are available.

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46 Phenobarbital, Primidone and Other Barbiturates

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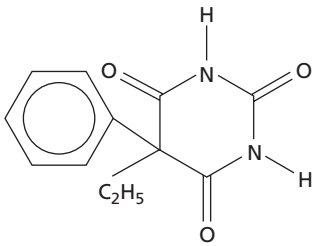

	Phenobarbital	Primidone
Primary indication	Adjunctive or first-line therapy for partial and generalized seizures (including myoclonus). Also for status epilepticus and neonatal seizures. Ineffective in absences	Adjunctive or first-line therapy for partial and generalized seizures (including myoclonus). Ineffective in absences
Usual preparations	Tablets: 15, 30, 50, 60 and 100 mg Elixir: 15 mg/5 mL Injection: 200 mg/mL	Tablets: 250 mg Suspension: 50 mg/mL
Usual dosage	*Oral*. Initial: 30 or 50 mg/day in adults and 3 mg/kg in children. Maintenance: 30–200 mg/day (adults); 3–8 mg/kg/day (children); 3–4 mg/kg/day (neonates). *Intravenous (status epilepticus)*. Adults: 10 mg/kg infused over 10 min or more (50–75 mg/min). Children and neonates 15–20 mg/kg at a rate of 100 mg/min. These doses may be followed by a maintenance daily dose of 1–4 mg/kg (adults) or 3–4 mg/kg (children and neonates)	*Adults and children > 9 years*. Initial: 62.5 mg at bedtime, to be increased gradually. Maintenance: 500–1000 mg/day. *Children < 9 years*. Initial: 50 mg at bedtime, to be increased gradually. Maintenance: 10–25 mg/kg/day
Dosing frequency	1–2 times/day	2–3 times/day
Significant drug interactions	Phenobarbital is an enzyme inducer and stimulates the metabolism of many other antiepileptic drugs and other drugs. Serum phenobarbital levels are increased by co-administration of valproic acid and some other drugs	Primidone is converted to phenobarbital and therefore interactions described with phenobarbital also apply to primidone. Enzyme-inducing drugs increase the phenobarbital–primidone ratio in serum. Isoniazid and nicotinamide increase serum primidone levels
Serum level monitoring	Although phenobarbital therapy can be adjusted solely on the basis of clinical response, measurement of serum drug concentrations may aid in selected cases	The target range for unchanged primidone has a merely indicative value. In most cases it is sufficient to monitor the serum concentration of metabolically derived phenobarbital

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	Phenobarbital	Primidone
Reference range	10–40 mg/L	3–12 mg/L
Common/important adverse effects	Sedation, ataxia, dizziness, insomnia, hyperkinesis (children), mood changes (especially depression), aggressiveness, cognitive dysfunction, impotence, reduced libido, folate deficiency, vitamin K and vitamin D deficiency, osteomalacia, Dupuytren's contracture, frozen shoulder, rash, other idiosyncratic reactions	Sedation, ataxia, dizziness, insomnia, hyperkinesis (children), mood changes (especially depression), aggressiveness, cognitive dysfunction, impotence, reduced libido, folate deficiency, vitamin K and vitamin D deficiency, osteomalacia, Dupuytren's contracture, frozen shoulder, rash, other idiosyncratic reactions
Main advantages	Broad-spectrum efficacy against many seizure types, feasibility of once-daily dosing and low cost	Broad-spectrum efficacy against many seizure types
Main disadvantages	Central nervous system adverse effects, enzyme induction	Central nervous system adverse effects, enzyme induction
Mechanism of action	Enhances chloride conductance at the $GABA_A$–benzodiazepine–chloride channel complex, depresses glutamate excitability, affects sodium, potassium and calcium conductance	Although primidone itself has anticonvulsant activity, much of its effect can be ascribed to metabolically derived phenobarbital. A possible contribution of phenylethylmalonamide to clinical effects has not been ascertained
Bioavailability	>95%	>90%
Time to peak levels after single dose	0.5–4 h	2.5–4 h
Main routes of elimination	About 25% of the dose is excreted unchanged in urine. The remainder is cleared by glucosidation and oxidation followed by conjugation	Partly excreted unchanged in urine and partly converted to phenylethylmalonamide (PEMA) and phenobarbital. Because phenobarbital has a much lower clearance, it accumulates
Volume of distribution	0.42–0.73 L/kg	0.64–0.72 L/kg
Elimination half-life	70–130 h (in adults; varies with age in children)	5–20 h (shortest values in children and in patients co-medicated with enzyme inducers)
Plasma clearance	2.1 to 4.9 mL/kg/h (in adults; varies with age in children)	35–52 mL/kg/h (adults, with highest values in patients co-medicated with enzyme inducers)
Protein binding	45–60%	10%
Active metabolites	None	Phenobarbital and phenylethylmalonamide (PEMA)
Comment	Highly effective antiepileptic drug, used as first-line therapy in many parts of the world because of its low cost. Because of its inferior tolerability to other drugs, particularly in children, it is rarely used as first line when cost is not the primary consideration	Because of its inferior tolerability to other drugs (particularly in children), primidone is rarely used as a first-line drug. However, it may be a useful third-line agent, particularly in patients with generalized seizures

Introduction

Barbiturates are a group of derivatives of barbituric acid, a compound synthesized from condensation of malonic acid and urea in 1864. Initially believed to have only sedative properties, barbiturates have been recognized as antiepileptic agents since 1912, when Hauptmann discovered serendipitously a dramatic reduction of seizure frequency in patients with bromide-resistant epilepsy treated with phenobarbital (phenobarbitone) [1]. Phenobarbital is the oldest antiepileptic drug (AED) still in use. Despite the development of successive generations of AEDs, phenobarbital has retained a unique role in the therapeutic armamentarium and is still the most commonly prescribed AED in the world. Because of its efficacy and low cost, it is recommended by the World Health Organization as first line for partial and tonic–clonic seizures in developing countries in all age groups [2]. Despite its sedative and behavioural effects, phenobarbital also remains a relatively commonly prescribed drug in many developed countries [3].

Over the years, attempts have been made to modify phenobarbital's molecular structure in order to identify agents with greater efficacy and lesser toxicity. Primidone was introduced into clinical practice in 1952 and is still relatively widely used. However, its effects can be attributed largely to metabolically derived phenobarbital. Additionally, two *N*-methyl derivatives of barbituric acid, methylphenobarbital (or mephobarbital) and metharbital, possess antiepileptic properties and were introduced into therapeutics in 1932 and 1948, respectively; neither drug, however, achieved widespread use. Barbexaclone, the propylhexedrine salt of phenobarbital, was marketed with the aim of decreasing the sedation associated with phenobarbital.

In this chapter, the comprehensive features of phenobarbital, primidone and other barbiturates will be outlined. A number of excellent reviews devoted to this subject are already available [4–14].

Phenobarbital

Chemistry

Phenobarbital (5-ethyl-5-phenylbarbituric acid) is a substituted barbituric acid with more potent anticonvulsant than sedative properties. Indeed, the presence of a phenyl group at the C-5 position confers relatively selective antiepileptic activity (Fig. 46.1). Phenobarbital has a molecular weight of 232.23; the free acid of phenobarbital is a white crystalline substance, soluble in non-polar solvents such as chloroform, ethyl ether, ethanol and propylene glycol, but relatively insoluble in water. In contrast, the sodium salt is freely soluble in water. Phenobarbital is a weak acid with a pK_a of 7.3, similar to the physiological pH of plasma. Changes in pH, which may occur in active epilepsy, can alter the ratio of ionized to non-ionized phenobarbital, resulting in significant modifications of its distribution and excretion [7].

Activity in animal models and mechanisms of action

In experimental models of epilepsy, phenobarbital seems to act in a relatively non-selective manner. It protects against maximal electroshock convulsions, subcutaneous pentylenetetrazole-induced clonic seizures and electrically kindled seizures [5]. It also appears to prevent seizures induced by a variety of chemicals (such as strychnine, thiosemicarbazide and bicuculline) and photic seizures in the baboon [15]. In contrast, phenobarbital worsens spike–wave discharges in animal models of absence seizures, such as γ-butyrolactone-induced spike–wave seizures and the lethargic (lh/lh) mutant mouse [16]. This pattern of activity in various anticonvulsant tests, and particularly its ability to limit the spread of seizure activity and to elevate seizure threshold, suggests utility in generalized tonic–clonic seizures and partial seizures in humans. This is borne out in clinical practice, and phenobarbital has proven value in controlling generalized tonic–clonic seizures, other generalized seizure types (but not absence seizures) and partial seizures.

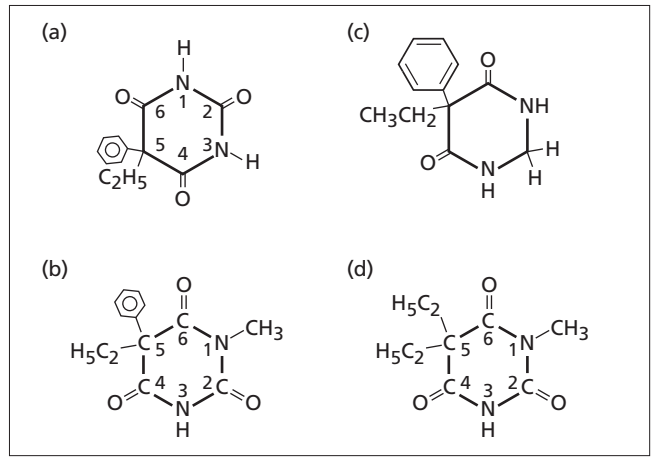

Fig. 46.1 Structural formulae of (a) phenobarbital, (b) methylphenobarbital, (c) primidone and (d) metharbital.

The possible mechanisms of action of phenobarbital are still not completely elucidated. Different effects are noted at different serum concentrations [4]. At high concentrations – such as those achieved in patients during treatment of status epilepticus – phenobarbital limits high-frequency repetitive firing of action potentials, possibly by interacting with Na^+ and K^+ transmembrane transport and conductance, and reduces cellular metabolism at the level of mitochondria or membrane ion gradients [17]. Phenobarbital also decreases the Ca^{2+} influx in presynaptic nerve endings, which could result in decreased release of excitatory neurotransmitters, such as glutamate and aspartate. However, these effects on ion transport appear to be more related to its sedative and/or anaesthetic properties than to its anticonvulsant action. At 'therapeutic' concentrations, phenobarbital produces modest changes in membrane conductance, but exerts its anticonvulsant action mainly by increasing postsynaptic γ-aminobutyric acid (GABA)-ergic inhibition [6].

Phenobarbital interacts with the $GABA_A$ receptor, which is a macromolecular complex containing binding sites for GABA, picrotoxin, neurosteroids, barbiturates and benzodiazepines and a chloride ion-selective channel [18]. GABA binds to $GABA_A$ receptors to regulate gating (opening and closing) of the chloride ion channel [18]. Studies indicate that phenobarbital acts mainly by increasing the mean channel open duration without affecting

channel conductances or opening frequency [19]; in contrast, the binding of a benzodiazepine to its allosterically coupled $GABA_A$ binding site increases opening frequency without affecting open or burst duration [19]. Interestingly, while benzodiazepines do not directly activate channels but only modify the GABA binding affinity, phenobarbital can directly promote channel opening in the presence and in the absence of GABA [20]. These small differences in mode of action can result in different effects: for example, phenobarbital could indiscriminately enhance all $GABA_A$ receptors, whereas benzodiazepines could exert a selective action on those with heavy firing activity, as occurs during a seizure [6]. A molecular basis for differential regulation of GABA receptor currents by barbiturates and benzodiazepines has also been established by studying $GABA_A$ receptor subunits [21]. In particular, it has been observed that $GABA_A$ receptors formed from α_1–β_1 subunits are sensitive to barbiturates but insensitive to benzodiazepines, whereas the transient co-expression of the γ_2, α_1 and β_1 subunits results in sensitivity to both benzodiazepines and phenobarbital [21]. This differential expression and assembly of various subunit subtypes in various cerebral regions – which is genetically determined [22] – could explain differences in the clinical profile between barbiturates and benzodiazepines.

Pharmacokinetics

Absorption

Phenobarbital can be administered by the intravenous, intramuscular and oral routes. Because free acid phenobarbital is poorly water soluble, formulations for intravenous and intramuscular administration are prepared from the sodium salt in slightly alkaline solutions.

Phenobarbital is readily absorbed after oral or intramuscular administration (Fig. 46.2) and peak plasma levels are linearly related to dose within a wide range of doses [7,23]. Times to peak plasma concentrations range between 0.5–4 h after oral dosing and 2–8 h after intramuscular injection [7,23–25]. As a whole, the differences between oral and intramuscular absorption are not statistically significant. In newborns (<6 weeks old) and premature babies, however, the absorption of orally administered phenobarbital is delayed and incomplete when compared with the intramuscular route. Jalling [26] found that 90% of the peak plasma concentration of phenobarbital was achieved within 4 h in 8 of 10 neonates following intramuscular injection, but in only 3 of 6 newborns after oral administration.

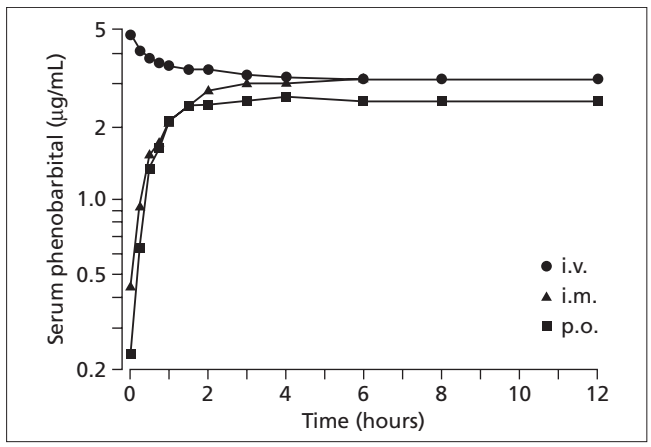

Fig. 46.2 Mean serum phenobarbital levels in six healthy volunteers after single intravenous and intramuscular injections of phenobarbital sodium 130 mg and single oral doses of phenobarbital acid 100 mg. Doses were given at least 1 month apart. From ref. 25 with permission.

The rate and extent of gastrointestinal absorption after oral dosing may also be influenced by other factors [7]. In the acid environment of the stomach, phenobarbital is largely non-ionized and diffusible. The bulk of orally administered phenobarbital, however, is absorbed in the small intestine, where the non-ionized fraction is smaller but intraluminal dwell time is longer. Characteristics of the preparation administered (e.g. free acid or salt, crystal size), gastric blood flow, gastric emptying time, gastric acidity, presence of food and neutralizing agents, and small intestine disorders may all alter phenobarbital absorption. Phenobarbital has a nearly complete bioavailability in humans, usually greater than 95% with a range from 80% to 100%, whether administered by the oral or intramuscular route [7,24,25].

Distribution

Phenobarbital distributes rapidly to all body tissues. Since its pK_a is similar to the physiological plasma pH, distribution processes are very sensitive to variations in the plasma pH. Acidosis results in a higher percentage of non-ionized phenobarbital, enhancing its diffusion from plasma to tissues. On the other hand, alkalosis causes an increased transfer of phenobarbital from tissues to plasma.

In infants, children and adults, phenobarbital is 45–60% bound to plasma proteins [27]. Binding in newborns is lower (36–43%) [26]. Changes in the extent of phenobarbital binding, as they may occur due to hypoalbuminaemia or displacement by other agents, are small and have little effect on unbound phenobarbital levels. The concentrations of phenobarbital in cerebrospinal fluid are 43–60% (in adults) and 48–83% (in infants) of plasma concentrations and correlate well with the unbound phenobarbital levels in plasma [7]. They also provide a reliable index of the phenobarbital concentration in brain. The brain to plasma concentration ratios in human epileptic brain specimens vary widely, ranging from 0.35 to 1.13 [7]. Phenobarbital concentrations are higher in cerebrospinal fluid than in saliva, and saliva to total plasma concentration ratios in infants range from 0.21 to 0.52 [7].

Phenobarbital rapidly crosses the placenta, so that maternally derived plasma phenobarbital concentrations in neonates are similar to those in the mother. Phenobarbital is also secreted in breast milk, in which its concentrations are about 40% of those in plasma [7,28].

After intravenous administration, phenobarbital distribution into body tissues is biphasic. In a first phase, the drug distributes rapidly into highly perfused organs including liver, kidney and heart, but not into the brain. During the second phase, phenobarbital achieves a fairly uniform distribution throughout the body except the fat tissue. This pattern of relatively slow entry into brain (12–60 min) and late exclusion from fat is related to phenobarbital's low lipid solubility; however, in status epilepticus, because of focal acidosis and increased cerebral

blood flow, the transfer of phenobarbital to the brain is much faster [7].

In adults, the volume of distribution of phenobarbital ranges from 0.36 to 0.73 L/kg [7]. The volume of distribution is larger in newborns, in whom it ranges from 0.39 to 2.25 L/kg after intravenous or intramuscular injection [29].

In some animal models, phenobarbital has been found to be a substrate of the efflux drug transporter P-glycoprotein, which is expressed at the cerebral capillary endothelium. The clinical relevance of this remains to be determined, but growing evidence seems to suggest that, by extruding AEDs from their intended site of action in the brain, overexpression of P-glycoprotein could play an important role in pharmacological intractability [30]. Expression of P-glycoprotein seems to be partly determined by genetic polymorphism of the encoding gene *ABCB1*, and the C3435T polymorphism of the *ABCB1* gene has been reported to influence the penetration of phenobarbital across the blood–brain barrier in patients with generalized epilepsy [31].

Elimination

Elimination of phenobarbital by all routes is slow and the average elimination half-life after single doses is between 70 and 130 h, the longest amongst frequently used AEDs [7,25]. Under usual circumstances, the plasma clearance of phenobarbital ranges from 2.1 to 4.9 mL/kg/h in adults [7,24,25,32]. Phenobarbital elimination follows first-order kinetics and thus is independent of concentration [33]. Several factors, however, contribute to variation in rate of elimination, including urinary pH and flow, age, nutritional state, drug interactions and hepatic or renal disease [7].

Phenobarbital is eliminated partly unchanged and partly as inactive metabolites. There is considerable inter- and intrasubject variability in the amount of phenobarbital excreted unchanged; however, single dose and steady-state studies have shown that excretion as unchanged drug accounts for approximately 20–25% of the total clearance (range, 7–55%) [7]. Urinary pH influences the passive reabsorption of phenobarbital from the distal tubule, which favours the transport of non-ionized compounds. Alkalinization of urine converts more drug to the ionized, non-diffusible form, thereby resulting in increased phenobarbital excretion. The opposite occurs with acidification of urine. Raising urinary pH to 8.0, with a corresponding plasma pH of 7.55, increases the fraction of ionized phenobarbital in renal tubular fluid from 69% to 86%. Renal clearance of phenobarbital is also enhanced by diuresis. These findings are the basis for the use of forced diuresis and urine alkalinization in overdose patients.

The majority of a phenobarbital dose is eliminated by hepatic metabolism. A major route of biotransformation is hydroxylation of the phenyl ring (aromatic hydroxylation) by cytochrome P450 (CYP) enzymes to produce *p*-hydroxyphenobarbital. This metabolite is excreted in urine partly in free form and partly conjugated with glucuronic acid. The sum of the free and conjugated metabolite accounts for 8–34% of the administered dose, with high intersubject variability. Hydroxylation is catalysed primarily by the isozyme CYP2C9, with minor contributions from CYP2C19 and CYP2E1. Genetic polymorphism of CYP enzymes affects their expression, and an influence of genetic polymorphisms of CYP2C9 and CYP2C19 on the clearance of phenobarbital has been reported in Japanese patients [34–36]. *N*-glucosidation is a more recently identified metabolic pathway, leading to the formation of a phenobarbital *N*-glucoside metabolite. The *N*-glucosidation pathway is not active at birth but becomes effective only after 2 weeks of life. This may be the main reason for the long phenobarbital half-life in newborns. Phenobarbital *N*-glucoside accounts for clearance of 6–30% of the dose. It has been suggested that phenobarbital *N*-glucoside undergoes significant breakdown to as yet unidentified derivatives; therefore, *N*-glucosidation could be a more important metabolic pathway than originally thought [7]. Other less important routes of biotransformation are epoxidation, aliphatic hydroxylation and hydrolysis [7]. Enterohepatic circulation and faecal excretion probably are not important contributors to phenobarbital disposition under usual circumstances. Oral administration of activated charcoal, however, increases the intestinal elimination of phenobarbital and may be used in phenobarbital overdose [37]. Although phenobarbital is a well-known inducer of hepatic metabolism, it does not induce its own metabolism in humans. In animals, however, considerable autoinduction has been observed.

Pharmacokinetics in special groups

Phenobarbital half-life varies with age. Whereas premature and full-term newborns have the longest phenobarbital half-lives (ranging from 59 to 400 h), infants aged 6 weeks to 12 months have the shortest. Pitlick *et al.* [29] observed that the half-life diminishes from an average of 115 h to 67 h between birth and the first month of life. Half-lives of 37–133 h were found in 33 infants older than 6 months after single doses in one study [38] and even shorter values (21–75 h) were reported in other studies [7]. Total clearance ranged between 5.3 and 14.1 mL/kg/h in nine children aged 8 months to 4 years [39].

The clearance of phenobarbital is moderately reduced in the elderly, but interindividual variation is considerable. Average clearance values were 2.5 mL/kg/h in a group of patients >40 years old compared with 4.9 mL/kg/h in patients 15–40 years old [40]. A more recent study showed that phenobarbital clearance declined from 4.1 mL/kg/h in adults aged 20–50 to 3.2 mL/kg/h in those over 65 years [41].

The half-life of phenobarbital was prolonged in a group of patients with liver cirrhosis (130 ± 15 h) compared with healthy subjects (86 ± 3 h) [42]. Phenobarbital clearance is increased in children with protein–energy malnutrition [7].

Drug interactions

There are no well-documented clinically significant pharmacodynamic interactions between phenobarbital and other drugs, except perhaps for the reciprocal potentiation of central nervous system (CNS) depressant effects between barbiturates, benzodiazepines and other CNS depressants. However, there are many pharmacokinetic interactions [8].

Effects of phenobarbital on the pharmacokinetics of other drugs

Phenobarbital is a potent inducer of various microsomal enzymes including the CYP isoforms CYP1A2, CYP2B6, CYP2C9,

CYP2C19 and CYP3A4, as well as glucuronyl transferases and epoxide hydrolase [43]. Induction of CYP enzymes by phenobarbital results from altered transcriptional regulation mediated by orphan nuclear receptors, including the pregnane X receptor and constitutive androstane receptors [8,44]. Most clinically relevant drug–drug interactions involving phenobarbital are the result of enzyme induction [8]. Enzyme induction is influenced to some extent by environmental factors (e.g. tobacco smoking, alcohol), age and genetic factors, as demonstrated by studies in mono- and dizygotic twins [45]. Because of these influences, the magnitude of induction caused by phenobarbital in individual patients is largely unpredictable.

Because microsomal enzymes are involved in the biotransformation of most therapeutic agents, patients taking phenobarbital metabolize at a faster rate a wide range of concomitantly administered medications. These include, amongst others, a number of analgesics (antipyrine, amidopyrine, paracetamol, meperidine and methadone), antiasthma agents (theophylline), calcium channel blockers (verapamil, nimodipine, felodipine, nisoldipine, nifedipine), antimicrobials (chloramphenicol, doxicycline, griseofulvin, metronidazole, some antiretroviral drugs), anticoagulants (bishydroxycoumarin and warfarin), antiulcer agents (cimetidine), immunosuppressants (ciclosporin), antineoplastic agents (taxanes, vinca alkaloids, cyclophosphamide, methotrexate, nitrosureas, teniposide, irinotecan), psychotropic drugs (chlorpromazine, haloperidol, clozapine, desipramine, nortriptyline, benzodiazepines), corticosteroids (cortisol, dexamethasone, methylprednisolone, hydrocortisone) and steroid oral contraceptives [8].

The metabolism of other AEDs is also stimulated by phenobarbital. Phenobarbital decreases the plasma concentrations of brivaracetam, carisbamate, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, monohydroxycarbazepine, primidone, rufinamide, stiripentol, tiagabine, topiramate, valproic acid and zonisamide [8,46]. The clinical significance of these interactions is often limited, because the partial loss of efficacy resulting from the decreased serum concentration of the affected drug tends to be compensated for by the antiepileptic effect of the phenobarbital added on [43]. However, in some patients, failure to achieve sufficient plasma concentrations of the affected drug may lead to inadequate seizure control. Phenobarbital may also cause a decline of plasma carbamazepine levels in some patients [8], but the effect is variable. The effect of phenobarbital on plasma phenytoin levels is complex: in particular, phenobarbital may simultaneously induce and inhibit phenytoin metabolism, and the prevailing effect in the individual patient is unpredictable [8].

Induction of drug metabolism by phenobarbital does not always result in a reduction of the effects of other drugs. There are instances in which the induction of metabolism causes an increased production of toxic metabolites of the affected drug, leading to increased toxicity. This is the case for acetophenitidin, whose induction of metabolism by phenobarbital may be responsible for methaemoglobin formation by increasing the production of a toxic intermediary metabolite (2-hydroxyphenetidin), particularly in patients with genetically determined metabolic deficiencies [47]. It has also been suggested that induction of the formation of toxic metabolites of valproic acid by phenobarbital may predispose to valproic acid hepatotoxicity [48].

Effects of other drugs on the pharmacokinetics of phenobarbital

Valproic acid, felbamate, clobazam, sulthiame, dextropropoxyphene, chloramphenicol and, to a lesser extent, phenytoin may inhibit phenobarbital metabolism, leading to elevation of phenobarbital levels. Accumulation of phenobarbital caused by valproic acid is the most constant, predictable and clinically important interaction in this group. The clinical manifestations include increasing somnolence, sometimes resulting in coma (an outcome for which a pharmacodynamic interaction may contribute), within days or weeks after the initiation of valproic acid administration. The increase in serum phenobarbital concentrations appears to be greater in paediatric patients (112.5%) than in adults (50.9%). Although the rate and magnitude of this interaction vary among individuals, phenobarbital dosage reductions are necessary in up to 80% of patients started on valproic acid comedication. The primary mechanism of this interaction involves decreased biotransformation to *p*-hydroxyphenobarbital by inhibition of CYP2C9 and/or CYP2C19 [49]. Furthermore, toxic signs may be precipitated by elevated blood ammonia levels, because the magnitude of valproic acid-induced hyperammonaemia is increased in patients co-medicated with phenobarbital.

The use of vigabatrin in combination with phenobarbital has sometimes been associated with a small but significant decrease in serum phenobarbital concentration. The mechanism of this interaction is unknown [8].

Serum level monitoring

Although phenobarbital dosage can often be individualized on the basis of clinical response alone, monitoring the serum concentration of the drug may be useful in selected indications (Chapter 9).

A therapeutic range of serum phenobarbital concentrations was first suggested by Buchthal *et al.* [50], who described 11 previously untreated patients with frequent seizures in whom phenobarbital was administered in small and gradually increased doses. The average level at which EEG and clinical response occurred was 10 mg/L. By pooling the data from four studies (three retrospective and one prospective) [51–54] in a total of 568 patients, Booker [10] found that 84% of the subjects who were controlled had plasma phenobarbital levels between 10 and 40 mg/L (Table 46.1). Some patients, however, experience good seizure control above or below this limit. As the plasma level increases above 40 mg/L, potential benefits must be weighed against the potential for adverse effects. Because of variable development of tolerance to some of the CNS adverse effects of phenobarbital, the upper limit of the therapeutic range is not well defined and varies among individuals.

The optimal plasma phenobarbital concentration also varies with seizure type. In a study of 78 patients with various seizure types, Schmidt *et al.* [55] reported that the plasma concentrations of phenobarbital required to produce complete control of simple or complex partial seizures were significantly higher than those required to control tonic–clonic seizures alone (38 ± 6 mg/L versus 18 ± 10 mg/L).

Table 46.1 Plasma phenobarbital levels versus seizure control. Pooled analysis of four studies (one prospective [51] and three retrospective [52–54]) in a total of 568 patients of different ages and with different seizure types who had achieved seizure freedom, mostly on monotherapy. The table shows the total number of subjects and the number controlled for each range of plasma levels as well as a cumulative percentage of the number of subjects who were controlled at progressively higher plasma levels.

Plasma phenobarbital level (mg/L)	Total number of subjects	Number of subjects controlled	Cumulative percentage of controlled subjects
<10	50	14	6.5
10–14	92	23	17.2
15–19	115	50	40.6
20–24	93	50	64.0
25–29	87	29	77.6
30–34	43	12	83.2
35–39	35	16	90.7
≥40	53	20	100.0

From ref. 10 with permission.

Efficacy

As is the case with other drugs marketed so long ago, phenobarbital efficacy is mainly documented by uncontrolled studies and case series, and information from controlled studies is relatively limited. There are, overall, extensive data indicating the value of phenobarbital in the treatment of both adult and childhood epilepsies. In controlled studies, efficacy has been demonstrated most clearly against partial and generalized tonic–clonic seizures [56], but there is general consensus that phenobarbital can be effective in controlling other generalized seizure types except for absence seizures.

Neonatal seizures and status epilepticus are two other well-established indications for the use of phenobarbital.

Adults and children with partial and generalized seizures

The most authoritative randomized double-blind controlled trial of phenobarbital in adults with epilepsy is the Veterans Administration (VA) Cooperative Study conducted by Mattson *et al*. [57] in the USA. In this study, the efficacy and tolerability of four drugs (phenobarbital, primidone, carbamazepine and phenytoin) were assessed in 622 adults with previously untreated or undertreated partial and secondary generalized tonic–clonic seizures. Phenobarbital, primidone, carbamazepine and phenytoin produced similar rates of overall seizure control (with percentages of 36%, 35%, 47% and 38%, respectively). While the prognosis for complete control of tonic–clonic seizures with the four drugs was also similar, carbamazepine provided significantly better total control of partial seizures (43%) than phenobarbital (16%) or primidone (15%), whereas phenytoin provided intermediate control (26%). These data were confirmed at every 6-month point during the 36 months of follow-up. To some extent, the lower response rates in patients with partial seizures randomized to phenobarbital or primidone could be explained by more patients in these groups exiting the trial because of adverse effects. In keeping with the data from this study, other open studies have shown phenobarbital to be as effective as carbamazepine and phenytoin in the treatment of predominantly tonic–clonic seizures, but with a higher failure rate in the management of partial seizures [55,58].

Two subsequent prospective randomized trials, one conducted in adults and one in children, have compared the efficacy and toxicity of phenobarbital, phenytoin, carbamazepine and valproic acid in newly diagnosed epilepsy in the UK. Patients entered the trial with a minimum of two previously untreated tonic–clonic seizures or partial seizures with or without secondary generalization. In the adult trial, which enrolled 243 patients, the overall outcome with all four drugs was good, with 27% remaining seizure free from the beginning and 75% entering 1 year of remission by 3 years of follow-up [59]. There were no significant differences in efficacy between the four drugs in either time to first seizure recurrence or time to achieve 1-year remission from all seizures. In the paediatric trial, which enrolled 167 children (aged 3–16 years), overall 20% of the patients remained seizure free and 73% achieved 1-year remission by 3 years of follow-up [60]. Although the authors claimed that there was no difference in efficacy between the drugs for either measure of efficacy at 1, 2 or 3 years of follow-up, only 10 children were allocated to phenobarbital because an excess of adverse effects precluded further recruitment of children in this arm of the study. The two UK studies included a larger proportion of patients with tonic–clonic seizures (including primary generalized) than with partial seizures alone, which explains their relatively good outcome in terms of seizure control. There has also been a number of other studies, either randomized or observational, performed in resource-restricted countries, confirming a substantial equivalence of effect of phenobarbital, carbamazepine and phenytoin in adults [9,61] and children [62,63], mostly with generalized tonic–clonic or partial seizures. These studies are described in some detail in the section discussing adverse effects.

The studies reviewed above indicate that phenobarbital is useful in the treatment of partial seizures (with and without secondary generalization) and primary generalized tonic–clonic seizures. The effects of phenobarbital in generalized seizures occurring within the spectrum of idiopathic generalized epilepsies have been also investigated. Phenobarbital has been shown to be effective in the treatment of idiopathic generalized epilepsy with tonic–clonic seizures [9,55,58,64,65]. Phenobarbital is also effective against other generalized seizure types, including myoclonic, clonic, atonic and tonic seizures, although evidence from well-designed randomized studies in these seizure types is lacking. Based on scattered reports and clinical experience, phenobarbital is ineffective against absence seizures and may even aggravate them [56].

Oral phenobarbital has also been used successfully to treat high-frequency tonic spasms in early infantile epileptic encephalopathy with suppression bursts [66]. It is also currently used in the treatment of progressive myoclonus epilepsies, mostly with the aim of suppressing motor seizures [67].

Neonatal seizures

Phenobarbital is traditionally considered the drug of choice for the treatment of neonatal seizures. This is primarily due to years of familiarity and experience with phenobarbital in children and adults. However, controlled evidence of its efficacy or superiority

Table 46.2 Phenobarbital efficacy in neonatal seizures.

Study	Number of patients	Response rate (%)	Loading dose (mg/kg)[a]
Lockman *et al*. [51]	39	32	15–20
VanOrman and Darrvish [68]	81	33	15–20
Painter *et al*. [69]	77	36	15–20
Gal *et al*. [70]	71	85	up to 40

Modified from ref. 71.
[a] Phenobarbital was given intravenously.

over other drugs is scanty. Moreover, neonatal seizures are a rather heterogeneous group of paroxysmal events and EEG confirmation of the diagnosis was remarkably absent in most studies.

Three case series show very close agreement on the efficacy of phenobarbital as the initial agent in the treatment of neonatal seizures [51,68,69]. In these open trials, involving a total of 197 neonates and utilizing intravenous loading doses of 15–20 mg/kg, seizure control was obtained in 32–36% of cases. Gal *et al*. [70], however, reported efficacy in 85% of 71 neonates in whom phenobarbital administered intravenously was used as monotherapy, at doses as high as 40 mg/kg to achieve or exceed plasma concentrations of 40 mg/L (Table 46.2). The lack of specific seizure definition, electrically or clinically, in all of these series makes the differences in outcome difficult to interpret [71].

Painter *et al*. [72] performed a randomized trial to assess the relative efficacy of phenobarbital and phenytoin in the treatment of seizures in neonates, using EEG criteria for diagnosis and to determine efficacy. Fifty-nine neonates with EEG-confirmed seizures mostly caused by asphyxia, or cerebral haemorrhage or infarction, were randomly assigned to receive either phenobarbital or phenytoin intravenously; the doses were sufficient to achieve free plasma concentrations of 25 mg/L for phenobarbital and 3 mg/L for phenytoin. Seizures were controlled in 43% of neonates assigned to receive phenobarbital and in 45% of neonates assigned to phenytoin. In refractory cases, the administration of phenobarbital and phenytoin in combination allowed control of seizures to be achieved in 32% of cases. Interestingly, the severity of seizures was a stronger predictor of the success of treatment than the assigned treatment.

High-dose phenobarbital therapy in newborns at term with severe perinatal asphyxia has been shown to improve neurological outcome. In a randomized prospective study with a 3-year follow-up, phenobarbital administered at a dose of 40 mg/kg intravenously was associated with a 27% reduction in the incidence of seizures and a significant improvement in neurological outcomes at 3 years of age [73].

Status epilepticus

Phenobarbital is efficacious in established status, of both tonic–clonic and partial type. For this indication, it can be given intravenously in adults at a loading dose of 10 mg/kg at a rate of 50–75 mg/min, and in children and neonates at a dose of 15–20 mg/kg at a rate of 100 mg/min. These doses may be followed by a maintenance daily dose of 1–4 mg/kg (adults) or 3–4 mg/kg (children and neonates).

Although current trends for the first-line treatment of status epilepticus favour the use of lorazepam (or diazepam), followed, if required, by phenytoin, several studies have shown that phenobarbital can be as effective as other options. In a randomized, non-blinded clinical trial, 36 consecutive patients with convulsive status epilepticus were treated either with a combination of diazepam and phenytoin or with phenobarbital [74]. Phenobarbital was administered intravenously at a rate of 100 mg/min until a dose of 10 mg/kg was achieved. Diazepam (10 mg) was infused at 2 mg/min intravenously and phenytoin (18 mg/kg) was administered simultaneously at a rate of 40 mg/min. There were 18 episodes of status epilepticus in each group. The cumulative convulsion time was shorter for the phenobarbital group than for the phenytoin/diazepam group (median, 5 versus 9 min, $P < 0.06$) and the response latency was also shorter for the phenobarbital group (median, 5.5 versus 15 min, $P < 0.10$). This finding is in keeping with experimental data demonstrating that, although maximum brain to plasma concentration ratios of phenobarbital may not be achieved 60 min after administration, effective brain phenobarbital concentrations are achieved within 3 min [75].

The best evidence for the efficacy of phenobarbital in generalized convulsive status epilepticus stems from a 5-year, randomized, double-blind, multicentre trial which compared four intravenous regimens: diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg) and phenytoin (18 mg/kg) [76]. The study included 518 patients with either overt generalized convulsive status epilepticus or subtle status epilepticus. In the group of overt generalized convulsive status epilepticus (386 patients), lorazepam was successful in 64.9% of cases, phenobarbital in 58.2%, diazepam plus phenytoin in 55.8% and phenytoin in 43.6%. In the group of subtle status (134 patients), no significant differences among the treatments were detected. Despite a trend in favour of lorazepam, in an intention-to-treat analysis, the differences among treatment groups were not statistically significant in terms of either efficacy or tolerability, even on a 12-h and 30-day analysis after the status. These data indicate that phenobarbital can be a valuable option as initial intravenous treatment of tonic–clonic status, its major disadvantage being respiratory depression and the frequent need for intubation.

Special indications

Phenobarbital has been extensively used in the past for prophylaxis against recurrence of febrile seizures; however, the potential adverse effects associated with continuous anticonvulsant treatment in children outweigh the relatively minor risks associated with simple febrile seizures, and this has led to a decline in the use of phenobarbital for this indication. Long-term pharmacological prophylaxis is now currently considered in only a minority of cases of febrile seizures occurring in children with pre-existing neurological abnormalities, or manifesting as prolonged or focal attacks, associated with transient or permanent neurological deficits [9]. If phenobarbital is chosen for prophylaxis, it should not be utilized intermittently, but must be administered daily. Faero *et al*. [77] compared 59 patients, all younger than 3 years, with

72 untreated children, and found that the recurrence rate of febrile convulsions was 13% in the phenobarbital group compared with 20% in the control group. However, the risk of recurrence decreased to 4% in those children whose plasma phenobarbital levels were maintained between 16 and 30 mg/L. In a meta-analysis of the efficacy of various medications in the prevention of recurrent febrile seizures, the risk of recurrence was significantly lower in children receiving continuous phenobarbital therapy than in those receiving placebo [78].

Phenobarbital has also been used in the treatment of seizures complicating cerebral malaria. In a randomized study performed in Kenya, 340 children were assigned to receive either a single intramuscular dose of phenobarbital (20 mg/kg) or an identical placebo [79]. Seizure frequency was significantly lower in the phenobarbital group than in the placebo group (11% versus 27%), but mortality was doubled (18% versus 8% deaths) in the phenobarbital group. Mortality due to respiratory arrest was greatly increased in children who received phenobarbital plus three or more doses of diazepam. The authors concluded that 20 mg/kg phenobarbital as a single intramuscular dose should not be recommended in this population because of an unacceptable risk of mortality, but this conclusion has not been shared by other investigators [80].

Adverse effects

After almost a century of worldwide use, phenobarbital is considered a relatively safe drug, particularly because it causes relatively few systemic or idiosyncratic adverse effects. However, its adverse effects on cognition and behaviour represent a common problem in daily practice. Overdose is also a specific concern with phenobarbital. A summary of the adverse effects of phenobarbital is given in Table 46.3.

Table 46.3 Adverse effects of phenobarbital.

Neurotoxicity
Sedation
Behavioural changes
Depression
Cognitive impairment
Decreased libido and potency
Dysarthria, ataxia, nystagmus[a]
Overdose[b]
Dependence and withdrawal symptoms[c]
Connective tissue disorders
Dupuytren's contracture
Frozen shoulder
Shoulder–hand syndrome
Metabolic bone disorders
Hypocalcaemia
Rickets and osteomalacia[d]
Miscellaneous
Folate deficiency
Megaloblastic anaemia
Vitamin K deficiency[e]
Hypersensitivity reactions
Hepatotoxicity
Exacerbation of porphyria
Teratogenicity

[a] These symptoms appear more commonly at serum levels >40 mg/L.
[b] Overdose may result in coma and death.
[c] Typical in neonates born to mothers who received phenobarbital during pregnancy.
[d] May lead to higher incidence of bone fractures.
[e] May cause a coagulation defect in neonates born to mothers exposed to phenobarbital.

Central nervous system effects

Most of the adverse effects causing discontinuation of treatment with phenobarbital (or impacting negatively on quality of life) involve the CNS. Sedation, in particular, is the most common adverse effect associated with phenobarbital, particularly at the onset of treatment. In the VA Cooperative Study, two of three patients complained of sedation at one or more visits in the first year; acute sedation, however, was not more frequent with phenobarbital than with other drugs (i.e. primidone, carbamazepine or phenytoin), probably because of a cautious dose titration (32 mg as starting dose) [57]. In the study of Heller *et al*. [59] comparing the effects of four drugs (phenobarbital, carbamazepine, phenytoin and valproic acid) as monotherapies in adults with newly diagnosed epilepsy, phenobarbital was more likely to be withdrawn because of adverse effects. Drowsiness and lethargy were the main reasons for early withdrawal, but the initial dose was higher (60 mg/day) than in the VA study.

Some tolerance to sedation may develop, particularly if the drug is introduced and up-titrated gradually. A subgroup of 58 patients taking phenobarbital in the VA Cooperative Study was examined at every visit for the first 3 months (1, 2, 4, 8, 12 weeks) to assess the incidence of acute adverse effects and development of tolerance. Of the subgroup studied for tolerance, 33% of patients started on phenobarbital reported initial sedation, declining significantly to 24% by 12 weeks ($P < 0.04$). Evidence of tolerance was shown by decreasing sedation despite increasing phenobarbital concentrations from a mean of 18 mg/L at 2 weeks to 24 mg/L at 12 weeks [57].

Instead of sedation, which is common in adults, insomnia and hyperkinetic activity may occur in children and, less commonly, in elderly subjects, as a paradoxical effect. In a study by Wolf and Forsythe [81], of 109 children treated continuously with phenobarbital following their first febrile seizure, 42% developed behavioural disorders, primarily hyperactivity. The disturbance was not correlated with plasma phenobarbital concentrations. Hyperactivity improved in all children when phenobarbital was discontinued, and disappeared entirely in 73%. Behavioural disturbances associated with phenobarbital were more likely to occur in the presence of organic brain disease or deficits [82,83]. In another study, when compared with phenytoin, carbamazepine and valproic acid in newly diagnosed children with epilepsy, phenobarbital was associated with the highest withdrawal rate, behavioural problems being the main cause [60]. Interestingly, although several studies in developed countries have shown a high rate of behavioural effects with phenobarbital, studies in countries with limited resources suggest that phenobarbital may not be associated with excess behavioural problems, for example when compared with carbamazepine [14,61,63,84]. The overall tolerability profile which emerged from studies conducted in less developed countries is discussed below.

Problems with memory or compromised work and school performance can develop even in the absence of sedation and hyperkinetic activity, although these factors may play a contributory role. Changes in cognitive function have been measured by various standardized neuropsychological tests. A decrease in verbal and performance intelligence quotient (IQ) scores has been observed in children treated with phenobarbital compared with normal control subjects [82,85] or patients receiving valproic acid [85] or carbamazepine [82]. Memory and concentration scores, visuomotor performance and spatial memory, and short-term memory can also be significantly impaired in phenobarbital-treated subjects, especially children. Performance on vigilance tests requiring sustained effort may also be impaired, even after tolerance has developed [82].

Alteration of affect, particularly depression, has been associated with the use of phenobarbital in children [82]. Complex symptoms, including depression, apathy, impotence, decreased libido and sluggishness, are sometimes observed in adults [4]. In the VA Cooperative Study, decreased libido and/or potency was found to be more common in patients treated with phenobarbital or primidone than in those receiving carbamazepine or phenytoin [57].

During chronic therapy, dysarthria, incoordination, ataxia, dizziness and nystagmus may appear if serum levels exceed 40 mg/L. Dyskinesia and peripheral neuropathy are very rare effects induced by phenobarbital [4]. Worsening [56] or *de novo* appearance of absence seizures [86] have been reported with phenobarbital use in epileptic patients.

Central nervous system tolerability in studies conducted in resource-restricted countries

Three randomized clinical trials and several observational studies investigated the effects of phenobarbital in the treatment of epilepsy in resource-restricted countries.

Pal *et al.* [63] found no between-group difference in efficacy and tolerability (particularly in behaviour rating scores) among 94 children from rural areas of India randomized to phenytoin or phenobarbital. In a large study performed in rural Kenya in which 302 untreated paediatric and adult patients were randomized to receive phenobarbital or carbamazepine, the investigators also found no difference in the proportion of patients remaining seizure free after a 6- and 12-month follow-up period, and tolerability did not differ significantly between groups [61]. Banu *et al.* [87] performed a double-blind randomized controlled trial comparing the adverse effects of phenobarbital and carbamazepine in 108 children with generalized tonic–clonic or partial seizures in a Bangladesh clinic. The authors observed comparable efficacy and tolerability between the two drugs, and there was no excess of behavioural side-effects with phenobarbital.

An increasing number of observational studies performed in resource-restricted countries [88–92], reviewed by Kwan and Brodie in 2004 [14], seem to confirm a relatively good tolerability profile of phenobarbital when used in these settings. In general, these trials included largely unselected, untreated patients with a wide range of seizure types across all ages. A study published more recently was conducted in six rural areas of China and tested a model for the treatment of convulsive forms of epilepsy at primary health-care level [93]. The study included 2455 patients with 'generalized' tonic–clonic seizures who were given treatment with phenobarbital. Overall, 72% of patients who completed the 24-month treatment had a reduction in seizure frequency of at least 50% as compared with a 6-month baseline, with one-third (31.3%) having their seizure frequencies decreased by 75% and one-quarter (26.2%) being seizure free. It is unclear whether the relatively low proportion of seizure-free patients might reflect suboptimal compliance. Mild adverse effects were reported by 26.1% of patients, whereas severe adverse effects were present in only 0.3%. Only 1% of patients discontinued medication because of adverse effects. A detailed cost-effectiveness analysis in a sample of patients enrolled in this project demonstrated that use of phenobarbital was associated with a significant decrease in health-care costs, along with a marked clinical improvement [94].

Overall, the above data indicate that, at variance with the relatively high discontinuation rates for adverse effects reported in randomized clinical trials performed in developed countries, phenobarbital appears to be not only efficacious but also fairly well tolerated when used in resource-restricted countries. This discrepancy may be explained by a number of factors, such as methodological weaknesses of many of the studies (variable length of follow-up, problems with seizure classification, open-label designs), cultural differences in reporting adverse drug effects, and greater acceptability of adverse effects due to lack of alternative AEDs. A more favourable tolerability profile in resource-restricted countries might be also related to the use of lower doses than in trials conducted in developed countries [14,95]. These factors clearly need to be investigated in future studies.

Drug dependence and withdrawal symptoms

Prolonged use of phenobarbital is associated with physical dependence, with the appearance of withdrawal symptoms following abrupt discontinuation. A withdrawal syndrome may also be observed in neonates born to mothers who received phenobarbital during pregnancy. This includes hyperexcitability, tremor, irritability and gastrointestinal upset, and can last for days or even weeks.

An increase in seizure frequency, or seizure recurrence in previously controlled patients, may occur during or after phenobarbital discontinuation, and some evidence suggests that these events may not always be due to the underlying epilepsy, but may involve a drug withdrawal manifestation [82]. In these cases, generalized tonic–clonic seizures may occur even when the patient had previously experienced only partial seizures. Therefore, if a decision is made to stop phenobarbital therapy, the drug should be tapered gradually to avoid convulsive withdrawal seizures and, more importantly, convulsive status epilepticus.

Overdose

Among 27 deaths associated with barbiturate poisoning in Ontario from 1955 to 1964, phenobarbital levels detected in postmortem blood ranged between 23 and 189 mg/L [96]. Clinically, excessively high doses of phenobarbital first produce ataxia, dysarthria, nystagmus, incoordination and uncontrollable sleepiness. As the serum levels rise, these effects progress to stupor and coma (Fig. 46.3). Death is due to depression of cardiorespiratory function.

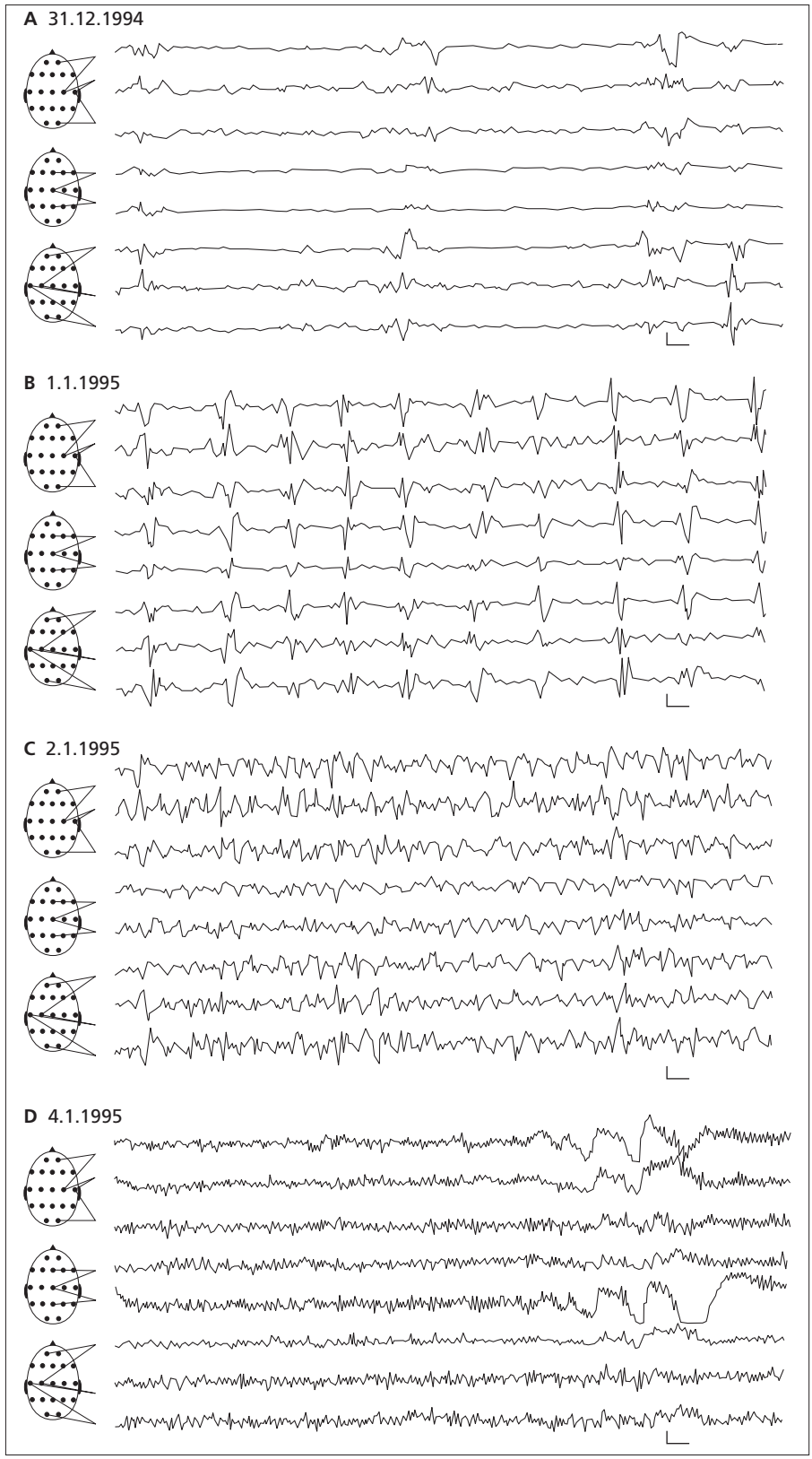

Fig. 46.3 Phenobarbital overdose in a 47-year-old woman with a 34-year history of focal motor and secondarily generalized seizures, on chronic treatment with phenobarbital 100 mg daily (usual plasma levels around 14 mg/L). There was no apparent aetiology for epilepsy. The patient was found comatose in her bed; on admission to the hospital, she was in deep coma and required assisted ventilation; the EEG showed a burst-suppression pattern (A). The plasma phenobarbital level was 82 mg/L. On the subsequent day, there was some improvement of the EEG, with shortening of the 'inter-burst' flattenings (B). The corresponding plasma level was 60 mg/L. Progressive improvement of the EEG (C), with a normal tracing on the fifth day (D) after overdose. When awake, the patient admitted to have taken 'many' pills to attempt suicide (R. Michelucci, personal observation).

The severity of CNS depression is much greater in drug-naive patients, in whom a level of 80 mg/L is considered potentially fatal [97]. Because of tolerance, some chronically treated patients do not report significant drowsiness or sedation even at serum levels that might cause coma in naive individuals. Concentrations above 70 mg/L, however, may compromise the level of consciousness in almost all individuals.

The EEG features of phenobarbital overdose reflect the clinical severity, evolving from burst suppression (Fig. 46.3) to electrical silence in fatal cases. In acute overdose patients, therapy includes maintenance of vital functions with assisted ventilation as well as enhancement of phenobarbital elimination with urine alkalinization and forced diuresis. Charcoal, ion exchange resins and haemodialysis have also been used [82,97,98].

Folate, vitamin D and vitamin deficiencies

Folate deficiency is relatively common in polymedicated patients, and phenobarbital monotherapy can also cause decreased folate levels and macrocytosis. Megaloblastic anaemia is rare, however, and the clinical significance of mild to moderate folate deficiency is uncertain.

Phenobarbital can affect calcium and bone metabolism, by inducing the catabolism of vitamin D. This usually causes decreased calcium absorption, low calcium levels and, sometimes, secondary hyperparathyroidism, rickets and osteomalacia, resulting in higher tendency to bone fractures [99]. Regular measurements of bone density and calcium and vitamin D supplements may be needed, particularly in high-risk populations such as people with poor exposure to sunlight, people with diets poor in vitamin D content and the elderly.

A severe coagulation defect has been reported in neonates born to mothers taking phenobarbital [100]. The coagulation defect is similar to that observed in vitamin K deficiency. Supplementation of vitamin K administered to mothers prepartum or to newborns at birth will prevent this complication [100].

Connective tissue disorders

Chronic phenobarbital treatment is associated with a higher incidence of Dupuytren's contracture with palmar nodules, frozen shoulder, plantar fibromatosis, Peyronie's disease, heel and knuckle pads and generalized joint pain. The incidence of barbiturate-related connective tissue disorders ranges from 5% to 38% depending on the population studied. Shoulder–hand syndrome was observed in 28% of 126 neurosurgical patients treated with barbiturates, but in none of 108 control patients receiving carbamazepine or phenytoin [101]. The condition can be reversible following early discontinuation of the barbiturate.

Exceptionally, phenobarbital has been associated with gingival hyperplasia [102].

Hypersensitivity reactions

Mild skin reactions, usually maculopapular, morbilliform or scarlatiniform rashes, occur in 1–3% of all patients receiving phenobarbital. Serious skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens–Johnson syndrome or toxic epidermal necrolysis, are rare. Although more common with phenytoin, instances of Stevens–Johnson syndrome or toxic epidermal necrolysis in patients taking phenobarbital while undergoing radiotherapy have been reported [103,104].

A barbiturate hypersensitivity syndrome, characterized by rash, eosinophilia and fever, is infrequent. Signs of hepatic injury (eosinophilic or granulomatous inflammation) may co-exist. Cases of bone marrow aplasia have also been reported, but they are very rare [105].

Systemic lupus erythematosus and acute intermittent porphyria may be unmasked or precipitated by phenobarbital [82].

Teratogenicity

Most studies of fetal outcome after prenatal AED exposure do not clarify the relative role of drugs, epilepsy, genetic and environmental factors. Overall, available studies indicate that intake of phenobarbital during pregnancy, as with other AEDs, is associated with an increased risk of malformations in the offspring. The risk is greater if phenobarbital is used in combination with other AEDs [106,107]. Data from the North American AED Pregnancy Registry showed that 6.5% of 77 children exposed to phenobarbital were born with major malformations, including cardiac defects (coarctation of the aorta with abnormal valves, tetralogy of Fallot, pulmonary atresia) and cleft lip and palate, suggesting a greater risk with phenobarbital exposure compared with exposures to different AEDs other than valproate [108]. Previous studies, however, yielded contradictory results, showing either no differences in fetal malformation rates with phenobarbital compared with other AEDs or even a possibly lower teratogenic profile [109]. Ongoing large prospective registries will hopefully better clarify the teratogenic risk of phenobarbital in the near future. More information on risks associated with the use of specific AEDs during pregnancy can be found in Chapter 25.

Place in current therapy

Phenobarbital has been marketed as either the acid or the sodium salt in 15-, 30-, 50-, 60- and 100-mg tablets, although not all strengths are available in all countries. Oral solutions (elixirs) are also available, as well as parenteral solutions, usually containing 100 or 200 mg of the sodium salt.

Initiation of therapy with phenobarbital should be gradual, with a starting dose in adults of 30 or 50 mg/day. The dose can be titrated by 30- to 50-mg increments every 1 or 2 weeks, according to tolerability. The usual maintenance dose ranges between 60 and 200 mg/day, but in most adults it is within the 90–120 mg/day range. Once-daily dosing is the most convenient mode of administration, particularly in adults.

In children, the starting dose is 3 mg/kg/day, which is titrated up to a maintenance dose of 3–8 mg/kg/day. Sometimes, a twice-daily dosing may be necessary due to the shorter half-life in children. Phenobarbital dosages in status epilepticus and neonatal seizures are discussed in Chapters 18 and 13, respectively.

Though not usually considered a first-line agent when cost is not a primary consideration, phenobarbital still plays a significant role in therapeutic practice. Clear advantages are low cost, ease of use, once-daily dosing, availability of different routes of administration (oral, intramuscular, intravenous), low risk of idiosyncratic reactions and efficacy against most seizure types. These characteristics render phenobarbital an important agent, particularly suitable for resource-restricted countries. Because of its long

half-life, phenobarbital can be suitable for specific categories of patients, such as those who are prone to short periods of non-compliance. Its main disadvantage consists in its potential to cause CNS adverse effects, particularly sedation in adults and behavioural changes in children. While its sedative effects may be minimized by slow titration and development of tolerance, behavioural changes need close monitoring. The enzyme-inducing effects of phenobarbital are also disadvantageous, particularly in patients requiring co-medications. Phenobarbital shows good efficacy in controlling tonic–clonic seizures, either primary or secondary generalized, and is also efficacious in other generalized seizure types, though it is ineffective against absence seizures. It is also efficacious against partial seizures, though to a lesser extent than carbamazepine. Neonatal seizures and status epilepticus are two other valuable indications. Aside from epilepsy, phenobarbital is also used at times in the management of increased intracranial pressure following severe brain injury, although it may not affect overall outcome in these patients [110].

Primidone

Chemistry

Primidone [5-ethyldihydro-5-phenyl-4,6-(1H,5H)-pyrimidinedione] is a deoxybarbiturate which differs from phenobarbital in lacking the carbonyl group in position 2 of the pyrimidine ring (Fig. 46.1). Primidone has a molecular weight of 218.25. It is an odourless crystalline white powder, with a slightly bitter taste and a melting point of 218–282°C. It is almost insoluble in water and organic solvents, but is somewhat soluble in ethanol [11,12].

Activity in animal models and mechanisms of action

Primidone's actions are largely mediated by its metabolite phenobarbital. Another active metabolite, phenylethylmalonamide (PEMA), might also play a role in the activity of primidone in animal models, though its contribution to clinical effects is unclear. Primidone itself, in any case, has independent anticonvulsant activity. Indeed, a single dose of primidone has been shown to protect rats against experimentally induced seizures before active metabolites become detectable in blood [111]. Similar protection has been demonstrated in mice when the biotransformation of primidone was delayed by pre-administration of a metabolic inhibitor [112].

Primidone is effective in preventing seizures induced by maximal electroshock, but is virtually inactive against seizures induced by pentylenetrazole or bicuculline [112]. The activity profile of primidone in some animal models resembles that of carbamazepine and phenytoin more than that of phenobarbital, which is active against both maximal electroshock- and pentylenetrazole-induced seizures [112]. Primidone and phenobarbital differ pharmacodynamically not only in anticonvulsant spectrum, but also in protective or therapeutic index. In terms of brain concentrations in mice, primidone was found to be 2.5 times less neurotoxic than phenobarbital, with a correspondingly higher therapeutic index [112].

In cultured mouse neurones, primidone had no effect on GABA and glutamate responses at concentrations up to 50 mg/L, but showed a synergistic action with phenobarbital to reduce sustained high-frequency repetitive firing [113].

Pharmacokinetics

Absorption

Primidone can only be administered orally, because its low solubility prevents parenteral administration. Time to peak plasma concentrations of primidone after oral ingestion of tablets ranged between 2.7 and 3.2 h in adults [11,12,114] and between 4 and 6 h in children [11,12]. The oral bioavailability of primidone seems to be virtually complete because approximately 92% of the daily dose was recovered in the urine as unchanged primidone or as metabolites in children.

Distribution

Primidone distributes throughout body tissues and fluids in a similar pattern and to the same extent as phenobarbital. In humans, variable brain to blood concentration ratios of primidone have been reported, ranging from 40% to 87% [11,12]; these discrepancies may be due to the timing of specimen collections. Primidone does not bind significantly to plasma proteins: the bound fraction ranges from 0% to 20% [11,12]. The volume of distribution of primidone has been estimated to be in the order of 0.64–0.72 L/kg in adults with epilepsy [11,12].

Elimination

Although the majority of an administered dose is excreted in the urine unchanged, primidone undergoes significant biotransformation. The primary and most relevant metabolic pathways involve (a) formation of PEMA by cleavage of the pyrimidine ring and (b) formation of phenobarbital by oxidation of the methylene group. Phenobarbital in turn is further metabolized, as previously discussed in this chapter. Other metabolites of primidone have been identified (i.e. α-phenylbutyramide, *p*-hydroxyprimidone and α-phenyl-*p*-butyrolactone), but they have no practical significance because of their low concentrations and lack of pharmacological activity. The time-course of appearance in plasma of the metabolites is different for PEMA and phenobarbital. After a first dose of primidone, PEMA was detected in blood within a few hours, whereas phenobarbital was often not measurable during the first 24 h [114].

Numerous clinical studies have addressed the quantitative aspects of the biotransformation of primidone to phenobarbital and PEMA. By comparing the level to dose ratios for phenobarbital and primidone in patients who had taken either drug for at least 6 months, Olesen and Dam [115] concluded that, on average, 24.5% of primidone administered was converted to phenobarbital. This finding was in keeping with the observation that, in order to achieve the same serum phenobarbital levels, the primidone dose (in mg/kg) has to be about five times higher than the corresponding dose of phenobarbital. Other studies, however, suggested that the proportion of a primidone dose converted to phenobarbital is lower. The biotransformation of primidone is influenced by enzyme-inducing AEDs such as phenytoin and carbamazepine, which increase the rate of conversion of primidone to phenobarbital (Table 46.4).

The elimination half-life of primidone is variable and may range from 3.3 to 22.4 h, with factors such as age and concomitant therapy accounting for much of the variability [11,12]. In

Table 46.4 Ratios of serum levels of primidone (PRM), phenobarbital (PB) and phenylethylmalonamide (PEMA) to primidone dose, and ratios of serum levels of primidone, phenobarbital and PEMA at steady state. All blood samples were drawn before the first morning dose in hospitalized patients.

	n	Ratios of serum levels to PRM dose[a]			Ratios of serum levels[a]	
		PRM	PB	PEMA	PB/PRM	PEMA/PRM
Monotherapy	10	0.78 ± 0.25	1.47 ± 0.53	0.64 ± 0.39	1.65 ± 0.74	0.70 ± 0.36
Co-medication[b]	53	0.40 ± 0.15	2.40 ± 0.98	0.75 ± 0.42	5.83 ± 2.62	1.71 ± 0.75

From ref. 11 with permission.

[a] Mean ± SD; primidone dose in mg/kg/day, serum levels in mg/L.

[b] Co-medication consisted of phenytoin, carbamazepine or both.

adults co-medicated with enzyme-inducing AEDs, half-life values are generally in the range of 3.3–11 h [11,12,114]. The ability of newborns to metabolize primidone to phenobarbital appears to be very limited, and in neonates the half-life of primidone has been found to be 23 h on average, with a range of 8–30 h [11,12].

Drug interactions

Since primidone is metabolized to phenobarbital, interactions described for phenobarbital also apply to phenobarbital derived from primidone. In addition, primidone itself is the cause as well as the target of numerous pharmacokinetic interactions. In particular, the conversion of primidone to phenobarbital and PEMA may be induced and inhibited by other drugs.

A marked increase in the rate of biotransformation of primidone is caused by phenytoin [116]. Carbamazepine also accelerates the biotransformation of primidone, but to a lesser extent. Bourgeois [11] reviewed the effects of co-medication with phenytoin, carbamazepine or both on the concentration to dose ratio and on the ratios between the concentrations of primidone, phenobarbital and PEMA (Table 46.4). Compared with primidone monotherapy, morning trough levels of primidone were reduced by about 50% and, conversely, phenobarbital levels were raised by a factor of 1.6 in patients co-medicated with phenytoin and/or carbamazepine. Thus, when patients are taking phenytoin or carbamazepine, the average primidone dose required to achieve a given phenobarbital concentration is 1.6 times lower than with primidone monotherapy. In addition, the morning trough serum concentration ratio of phenobarbital to primidone is more than three times higher in co-medicated patients. This implies that the serum levels of phenobarbital may increase from 'therapeutic' to 'toxic' levels if phenytoin or carbamazepine is added to pre-existing primidone therapy.

Valproic acid may increase the levels of metabolically derived phenobarbital by inhibiting phenobarbital metabolism, and it may cause transient elevations of primidone levels. Isoniazid and nicotinamide have been shown to inhibit the conversion of primidone to phenobarbital, resulting in high levels of primidone.

The effects of primidone on the pharmacokinetics of other drugs are similar to those described for phenobarbital.

Serum level monitoring

There is a poor correlation between the oral dose of primidone and the plasma levels of primidone itself and its metabolite phenobarbital. The VA Cooperative Study [57] suggested that optimal plasma primidone levels are on average in the order of 12 mg/L with an associated phenobarbital level of 15 mg/L, which corresponds to a primidone to phenobarbital ratio of 0.8. However, a large variability occurs between patients, and co-medication with enzyme-inducing agents invariably lowers the primidone to phenobarbital ratio. Although a therapeutic range of about 3–12 mg/L has been suggested for primidone, monitoring primidone levels have very limited clinical value, and monitoring the levels of metabolically derived phenobarbital is more useful in guiding therapy.

Efficacy

Because primidone is metabolized to phenobarbital, there has long been a controversy as to whether primidone is simply a prodrug of phenobarbital or whether it conveys added advantages. Primidone generally has the same indications as phenobarbital.

A number of comparative open-label clinical studies of primidone and other AEDs (usually phenobarbital, phenytoin and carbamazepine) have been performed in patients with partial and secondary generalized seizures, mostly showing no significant differences in efficacy [11,12]. In one cross-over study, primidone and phenobarbital were compared sequentially in 21 patients at the Chalfont Centre for Epilepsy in the UK [117]. Similar phenobarbital levels were maintained during both therapies, and primidone treatment was found to be slightly more effective against generalized tonic–clonic seizures than phenobarbital treatment [117]. In the authoritative double-blind VA study which compared primidone, phenobarbital, carbamazepine and phenytoin in previously untreated or undertreated adults with partial and secondary generalized tonic–clonic seizures, primidone controlled tonic–clonic seizures similarly to phenobarbital, phenytoin and carbamazepine, but was less effective in controlling partial seizures than carbamazepine and had, overall, a poorer tolerability than the other drugs [57].

Primidone has been used as a first-line agent in the treatment of juvenile myoclonic epilepsy [118], but has been largely replaced by valproic acid and other AEDs for this indication. Owing to its ability to shorten the QT interval, primidone has been proposed as an agent of choice for epilepsy patients with QT prolongation [119].

Adverse effects

As for antiepileptic effects, it is difficult to separate the adverse effects of primidone from those of phenobarbital. It is usually

stated that primidone shares all the adverse effects of phenobarbital, both in adults and in children [11,12]. The same also applies to idiosyncratic adverse effects and potential teratogenicity. Birth defects described in the offspring of women who took primidone during pregnancy are not specific and include ventricular septal defects, microcephaly and poor somatic development [120].

What clearly distinguishes primidone from phenobarbital is the occurrence of acute, mostly transient, initial intolerance. Marked adverse effects, including drowsiness, dizziness, ataxia, nausea and vomiting, can occur in some individuals even after a single low initial dose of primidone, and may lead to early discontinuation of treatment. Early adverse events were responsible for the higher rate of treatment failures reported with primidone as compared with phenobarbital, phenytoin and carbamazepine in the VA Cooperative Study [57]. Since acute toxicity has been shown to occur before phenobarbital and PEMA are detected in blood, it must be caused by primidone itself. Tolerance to these adverse effects of primidone develops rapidly, however, in a matter of hours to days. There is also some evidence that phenobarbital produces a cross-tolerance to acute primidone toxicity, as patients on long-term phenobarbital therapy are less prone to experience the same degree of intolerance when first exposed to primidone [11].

Overdose

Primidone overdose causes signs of CNS depression, hypotonia, reduced deep tendon reflexes and marked crystalluria. Symptoms of CNS depression seem to correlate better with plasma and cerebrospinal fluid primidone levels than with phenobarbital or PEMA levels.

Place in current therapy

Because of the potential for initial acute adverse reactions, it is important to start primidone treatment with a small dose and to up-titrate it slowly. An average starting dose for an adult would be 62.5 or 125 mg at night, with increments every 3 days (or longer) up to a final daily maintenance dose of 10–20 mg/kg. Because of the relatively short half-life of primidone, it is recommended to divide the daily dose into three administrations, although the need for this has never been documented.

Primidone is an intriguing drug because of its metabolic profile. It is an AED in its own right, and also a phenobarbital prodrug. Most experts believe, as does the author, that the main antiepileptic action of primidone is due to metabolically derived phenobarbital. The contribution of primidone itself or PEMA to antiepileptic effects is controversial, but is likely to be minor. The efficacy and tolerability profiles of primidone do not differ significantly from those of phenobarbital, and there is little reason to prescribe primidone instead of phenobarbital. When used, primidone has the same indications as phenobarbital. Aside from epilepsy, the main indication of primidone is essential tremor, in which primidone produces greater therapeutic benefit than phenobarbital. Eight double-blind placebo-controlled studies reviewed by Koller *et al.* [121] have provided consistent evidence of efficacy of primidone (at doses ranging from 50 to 1000 mg/day), with tremor relief comparable to that achieved with β-adrenergic blockers.

Other barbiturates

Metharbital

Metharbital or 5,5-diethyl-1-methylbarbituric acid (Fig. 46.1) is less polar than phenobarbital and more lipid soluble. There has been little interest in this drug for many years. There are no consistent published data on its pharmacokinetics, clinical use and toxicity. Whether it has a role in contemporary therapeutic practice is debatable.

Methylphenobarbital (or mephobarbital)

Methylphenobarbital (5-ethyl-1-methyl-5-phenylbarbituric acid) is the *N*-methylated analogue of phenobarbital (Fig. 46.1). It is used as a racemic mixture containing equal parts of the R(–) and S(+) enantiomers, it has somewhat more lipophilic properties than phenobarbital, and it has a pK_a value of 7.8.

Methylphenobarbital is well absorbed from the gastrointestinal tract but it undergoes appreciable presystemic metabolism and its oral bioavailability is about 75% [122]. Methylphenobarbital has a mean apparent volume of distribution of about 2 L/kg in adults, which is higher than that of phenobarbital and correlates with the greater lipophilicity of the compound, favouring extensive distribution into tissues [5,13]. In human plasma, about 70% of the R-enantiomer and 60% of the S-enantiomer is protein bound.

In adults not being treated with other drugs, the half-life of racemic methylphenobarbital after the first oral dose averages 49 ± 18.8 h, but is significantly shortened (19.6 ± 5 h) in patients co-medicated with enzyme-inducing agents [5,13]. The two enantiomers have different half-lives, 7.50 ± 1.7 h for the R-enantiomer and 69.8 ± 14.8 h for the S-enantiomer after a single oral dose. These differences reflect different clearance values, which are in the order of 0.4 ± 0.18 L/kg/h for the R-enantiomer and 0.017 ± 0.001 L/kg/h for the S-enantiomer. Methylphenobarbital is cleared almost entirely by biotransformation, and only 1.5–3% of an orally administered dose is excreted unchanged in urine [13]. Biotransformation is stereoselective. The R-enantiomer is metabolized mainly by CYP2C19-mediated aromatic hydroxylation leading to the formation of phenolic, diol and O-methylcatechol derivatives, and to a lesser extent is converted by other enzymes to phenobarbital. On the other hand, the S-enantiomer is mainly dealkylated to phenobarbital, though a small amount of hydroxylation also occurs. In subjects with genetically determined CYP2C19 deficiency, the fraction of the R-enantiomer converted to phenobarbital increases substantially, leading to more extensive phenobarbital accumulation.

The therapeutic and adverse effects of methylphenobarbital appear to be mediated largely by metabolically derived phenobarbital, the plasma concentrations of which at steady state are 3–10 times higher than those of the parent drug. Enzyme-inducing AEDs stimulate the conversion of methylphenobarbital to phenobarbital. Otherwise, drug interactions with methylphenobarbital are likely to reflect those observed with phenobarbital. Methylphenobarbital also has the same indications as phenobarbital and, in nearly all clinical situations, phenobarbital and methylphenobarbital may be considered interchangeable. The tolerability profile of methylphenobarbital is also substantially indistinguishable from that of phenobarbital.

Methylphenobarbital has been marketed as 30-, 60- and 200-mg tablets. Considerations concerning dose titration, daily dosing and optimal plasma concentrations are the same as for phenobarbital, except that, to obtain equivalent phenobarbital levels, 1.7–2.0 mg of methylphenobarbital should be prescribed for each milligram of phenobarbital. The higher dosage requirement is due to the need to compensate for the rapid elimination of *R*-methylphenobarbital.

Although phenobarbital and methylphenobarbital are virtually interchangeable, an argument has been raised for preferring methylphenobarbital to phenobarbital. Within the range of plasma concentrations of phenobarbital encountered therapeutically, the relationship between steady-state plasma concentrations of phenobarbital and methylphenobarbital dose is linear, whereas at times some deviations from linearity can be observed in the relation between plasma phenobarbital levels and phenobarbital dose [123]. Therefore, plasma concentrations of phenobarbital might be adjusted more predictably in patients taking mehylphenobarbital than in those taking phenobarbital itself.

Barbexaclone

Barbexaclone is the propylhexedrine salt of phenobarbital. These two ingredients are contained in the proportions of 60% and 40%, respectively. Propylhexedrine is intended to act as a CNS stimulant in order to antagonize the sedative properties of the barbiturate.

The pharmacokinetics of phenonobarbital were compared after oral administration of equimolar doses of the drug as the acid or as the propylhexedrine salt in healthy volunteers. Absorption and elimination parameters were very similar and it was concluded that propylhexedrine does not affect the pharmacokinetics of phenobarbital given as barbexaclone [124].

There has been a considerable interest in the use of barbexaclone, mostly in the Italian and Spanish literature. Several reports, mostly based on small series of patients receiving barbexaclone as add-on or first-line agent, or after switching from phenobarbital therapy, have claimed that barbexaclone is at least as effective as phenobarbital but better tolerated, with less sedative properties in both adults and children. The more favourable tolerability profile was attributed to the psychostimulant effect of propylhexedrine. These promising results, however, were mostly published in the 1970s and 1980s, and still await confirmation in controlled trials.

Barbexaclone is available as 25- and 100-mg tablets. Considerations concerning dose titration, daily dosing and optimal plasma concentrations are the same as for phenobarbital, except that, to obtain equivalent phenobarbital levels, 100 mg of barbexaclone is equivalent to 60 mg of phenobarbital.

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47 Phenytoin

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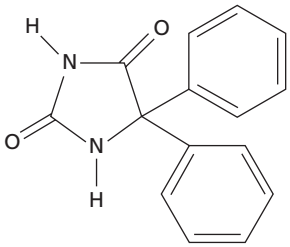

Primary indications	First-line or adjunctive therapy for partial and generalized seizures (except for myoclonic and absence seizures) and convulsive status epilepticus
Usual preparations	Capsules and tablets: 25, 30, 50, 100, 200 mg; chewtabs: 50 mg; liquid suspension: 30 mg/5 mL, 100 mg/5 mL; injection: 250 mg/5 mL
Usual dosages	Orally: 5 mg/kg/day (adults), 10 mg/kg/day (children); lower or higher maintenance doses may be needed, guided by serum level monitoring and clinical response
Dosing frequency	1–2 times/day
Significant drug interactions	Phenytoin is an enzyme inducer and may reduce the serum levels and clinical effect of many other drugs. Numerous drugs may interfere with phenytoin absorption, plasma protein binding, and metabolic elimination
Serum level monitoring	Useful
Target range	Total serum concentration: 10–20 mg/L (40–80 μmol/L). Unbound serum concentration (1–2 mg/L (4–8 μmol/L)
Common/important side-effects	Ataxia, dizziness, lethargy, sedation, headache, cognitive dysfunction, dyskinesia, acute encephalopathy, cutaneous and systemic hypersensitivity reactions (including fever, lymphadenopathy, liver toxicity, blood dyscrasias, vasculitis), gingival hyperplasia, folate deficiency, megaloblastic anaemia, vitamin K deficiency, decreased immunoglobulins, mood changes, depression, coarsened facies, hirsutism, acne, peripheral neuropathy, osteomalacia, hypocalcaemia, hormonal dysfunction, loss of libido, connective tissue alterations, pseudolymphoma, myopathy, teratogenic effects
Main advantages	Highly effective and inexpensive
Main disadvantages	Central nervous system and systemic adverse effects; non-linear elimination kinetics
Mechanisms of action	Blockade of voltage-dependent sodium channels
Oral bioavailability	95%
Time to peak levels	4–12 h
Elimination	Hepatic oxidation and hydroxylation, then conjugation
Volume of distribution	0.5–0.8 L/kg
Elimination half-life	7–80 h, dependent on serum level (mean, 20 h at 10–20 mg/L)
Plasma clearance	0.003–0.02 L/kg/h in adults (dependent on serum level), higher in children

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Michaelis constant (K_m)	~6 mg/L (24 μmol)
Maximum velocity of elimination (V_{max})	Adults 6–16 mg/kg/day; children higher
Protein binding	~90%
Active metabolites	None
Comment	Well-established first-line therapy. Its adverse effects profile and non-linear kinetics may make it a less desirable first-line therapy than other drugs in most patients

Introduction

Phenytoin was the first effective antiepileptic substance developed from systematic scientifically based screening, rather than from chance discovery. The molecule was synthesized early in the 20th century but, being less sedative than the bromides and phenobarbital, was not considered for an antiepileptic role until Putnam and Merritt, in the late 1930s, sought from various chemical suppliers substances with molecular structural resemblances to phenobarbital and which also contained phenyl substituents. It was then thought that an aromatic ring substituent probably enhanced any antiepileptic properties present in members of a family of molecules, as was the case for the barbiturates [1]. The substances supplied were tested in an animal model of convulsive epileptic seizures where phenytoin proved to combine antiseizure efficacy with a relative lack of sedation. Almost two-thirds of a century after its introduction into therapeutics, the drug remains extensively used worldwide, and has served as the paradigm for the development of many of the antiepileptic drugs (AEDs) which have subsequently been marketed. Several accounts of the discovery of phenytoin are available [1,2].

Chemistry

Phenytoin (5,5′-diphenylhydantoin) is usually supplied for therapeutic use as the free acid (molecular weight 252.3) or, more often, as the sodium salt (molecular weight 274.3). It is a white crystalline, relatively poorly water-soluble acidic substance (pK_a ~ 8.4). The sodium salt is more water soluble than the free acid, and is usually supplied in capsules or as a parenteral injection (pH ~ 12). The corresponding free acid is available in tablets or an oral suspension. Milligram for milligram, sodium phenytoin preparations contain about 8% less active substance than preparations containing phenytoin as the free acid.

There are many methods for measuring phenytoin at therapeutic concentrations in humans. The early methods were chemical or spectrophotometric, but, currently, phenytoin concentrations are usually measured by various immunoassays or, if other AEDs are to be measured simultaneously, by chromatographic methods, mainly high-performance liquid chromatography. Electrokinetic assays also exist.

Pharmacology

Anticonvulsant activity in experimental models

Phenytoin prevents or reduces the severity of induced seizures in various animal models of convulsive epileptic seizures (notably in the maximal electroshock model). It is also effective in models of partial (localization related) epileptic seizures, for instance electrically or chemically induced kindled focal seizures in rats [3]. It is relatively ineffective against generalized seizures induced by systemically administered chemical convulsants and in what were previously considered animal models of absence seizures (e.g. pentylenetetrazole-induced seizures) but which are now probably better regarded as models of myoclonic seizures. The drug is also ineffective in more recently developed and more realistic animal models of absence seizure, for instance the lethargic mouse and the Genetic Absence Epileptic Rat of Strasbourg (GAERS) [3].

Mechanisms of action

The antiepileptic effect of phenytoin at therapeutic relevant concentrations is thought to depend on its capacity to bind to, and prolong the inactivation of, mammalian, voltage-dependent sodium channels in neuronal cell membranes [4]. This effect is greater when the cell membrane is depolarized than when it is hyperpolarized. With repeated depolarizations, the ion channel block becomes use dependent. Phenytoin binds to the same site on the outer surface of the sodium channel as carbamazepine and lamotrigine [5]. However, phenytoin and carbamazepine have different binding site affinities and quantitatively, though not qualitatively, possess somewhat different actions [4]. Inactivation of voltage- and frequency-dependent sodium channels makes partly depolarized axons less capable of transmitting rapid trains of action potentials (as occur in epileptic discharges), but interferes less with axonal lower impulse frequency action potential traffic.

Phenytoin at high concentrations may also inhibit axonal and nerve terminal calcium channels. This action could stabilize axonal cell membranes and diminish neurotransmitter release at axon terminals in response to action potentials. The drug has no effect on T-type calcium channels in the thalamus, important in the genesis of absence seizures [4]. At high concentrations, phenytoin inhibits calcium/calmodulin-mediated protein phosphorylations [6]. The drug increases chloride conductances at

$GABA_A$ receptors, though whether this process contributes to its antiepileptic effects is unclear. Phenytoin is a weak dopamine antagonist.

Phenytoin's inhibition of axonal fast action potential traffic results in various well-documented electrophysiological effects, for example preventing post-tetanic potentiation of synaptic transmission in experimental preparations [7] and tending to prevent spike discharges spreading rather than suppressing their formation at experimental epileptic foci.

Pharmacokinetics

In recent times, little has been added to the knowledge of the pharmacokinetics of phenytoin that was available a decade or more ago [8–10]. Therefore, in the following account, references are cited mainly for more recently established facts.

Absorption

The absorption rate of phenytoin from different oral preparations may vary, but the absorption is not affected by food. Phenytoin bioavailability was reviewed in some detail by Neuvonen [11]. The importance of formulation was demonstrated 40 years ago when the oral bioavailability of phenytoin in the market leader's capsule formulation in Australasia was compromised due to an interaction between the drug in the capsule and the excipient calcium sulphate. Since then, the usual branded preparation has a lactose excipient. In this formulation, phenytoin has a consistent and complete, or nearly complete (~95%), oral bioavailability. Nonetheless, there are still reports of generic phenytoin tablets whose oral bioavailabilities appear incomplete and, to an extent, inconsistent [12]. Storage of phenytoin capsules under conditions of high temperature and humidity may reduce the oral bioavailability of the drug. Earlier reports suggested that the bioavailability of orally administered phenytoin was impaired during pregnancy, but subsequent studies showed that this was not so [13]. Variations in bioavailability should be unimportant clinically, provided the same preparation of the drug is always used by each patient. At least in the elderly, however, it has been suggested that day-to-day variation in phenytoin bioavailability may contribute to unexplained interindividual variability in serum phenytoin levels in patients stabilized on a constant dosage [14].

Phenytoin is absorbed very slowly and inconsistently from intramuscular injection sites, making this route of administration unsatisfactory in clinical practice. Fosphenytoin, a phenytoin prodrug which is water soluble and well absorbed after intramuscular administration, may be more conveniently used if the intramuscular route is needed [15]. Intravenous phenytoin is fully bioavailable, but the highly alkaline pH of the solution, and its content of polyethylene glycol, require very slow administration to minimize unwanted effects. The drug may crystallize out if injected into an intravenous fluid reservoir containing a solution at a more physiological pH. Fosphenytoin does not need to be dissolved in alkaline organic solvents, and offers some tolerability advantages over phenytoin for intravenous use [15].

The rectal bioavailability of phenytoin is low, around 24% ± 3%.

Distribution

After absorption, phenytoin is distributed throughout total body water, with relatively little selective regional concentration. Published values for the drug's apparent volume of distribution in humans have usually been in the range of 0.5–0.8 L/kg. In the brain, phenytoin achieves a slightly higher concentration than in serum. At steady state, it is present at a higher concentration in white than in grey matter, though soon after administration its concentration is temporarily higher in grey matter. Phenytoin is transported out of the brain by a P-glycoprotein mechanism, the increased activity of which may cause treatment resistance [16].

In whole blood, the phenytoin concentration in red cells is lower than in serum. Therefore, whole blood phenytoin concentrations are lower than simultaneously measured serum (or plasma) phenytoin concentrations. Some 90% of the drug in plasma is bound to plasma proteins, mainly albumin. The unbound fraction of the drug in plasma is higher in the neonate than in the adult, and increases a little with advanced age, in late pregnancy, and in the presence of hypoalbuminaemia (as occurs in malnutrition, liver disease, nephrotic or uraemic states, AIDS) and with high levels of glycated albumin, as in diabetics. Phenytoin concentrations in cerebrospinal fluid and routinely collected saliva, tears and sweat are very similar to the unbound phenytoin concentrations in plasma. However, the saliva phenytoin concentration varies with saliva flow rate and gum disease [17]. Certain acidic drugs, for example salicylates, valproic acid and various endogenous substances (fatty acids, bilirubin), can displace phenytoin from its plasma protein binding sites. Such displacements are rarely important clinically, but they must be kept in mind when total serum phenytoin concentrations are used as a guide to dosage adjustments. In fact, in the presence of an increased unbound fraction, therapeutic and toxic effects will occur at total phenytoin concentrations that are lower than usual.

Phenytoin concentrations in maternal milk are lower (~19%) than those simultaneously present in whole plasma, and vary to an extent with the fat and protein content of the milk. A breast-fed infant is unlikely to receive enough phenytoin from breast milk to experience adverse effects, unless the mother is very substantially overdosed with the drug.

Elimination

Less than 5% of a phenytoin dose is excreted in urine unmetabolized. The main known metabolic pathways for the drug are indicated in Figures 47.1 and 47.2. Nearly all of the body's metabolism of the drug appears to occur in the liver, though some conversion of phenytoin to its major metabolite, *p*-hydroxyphenytoin, occurs in the gums and perhaps in other peripheral tissues, for example neutrophil leucocytes and skin.

The major metabolite of phenytoin found in urine, *p*-hydroxyphenytoin (5-phenyl,5′-*p*-hydroxyphenylhydantoin, HPPH), present mainly in the form of its O-glucuronide conjugate, accounts for some 60–80% of usual doses of the drug. The glucuronidation is catalysed by UDP glucuronosyl transferase 1A isoforms [18]. *p*-Hydroxyphenytoin is formed via a postulated short-lived arene oxide intermediate in a reaction catalysed by the CYP450 (CYP) isoforms CYP2C9 and CYP2C19 (Fig. 47.1), and in the skin, possibly by CYP2C18 [19]. At conventional dosages, CYP2C9 activity accounts for some 90% of the hydroxylation of

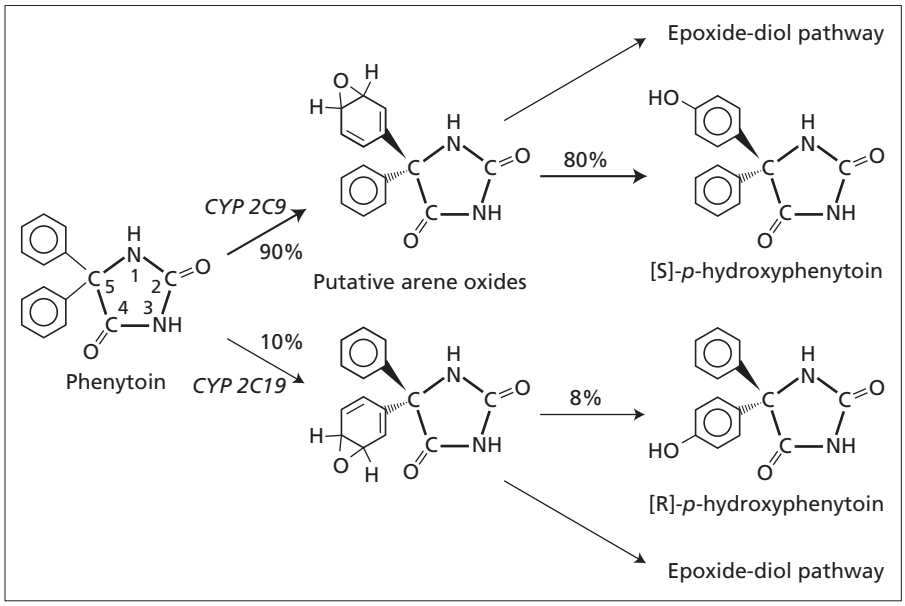

Fig. 47.1 Formulae for phenytoin and its known and putative stereoisomeric metabolites along the drug's major biotransformation pathway to *p*-hydroxyphenytoin.

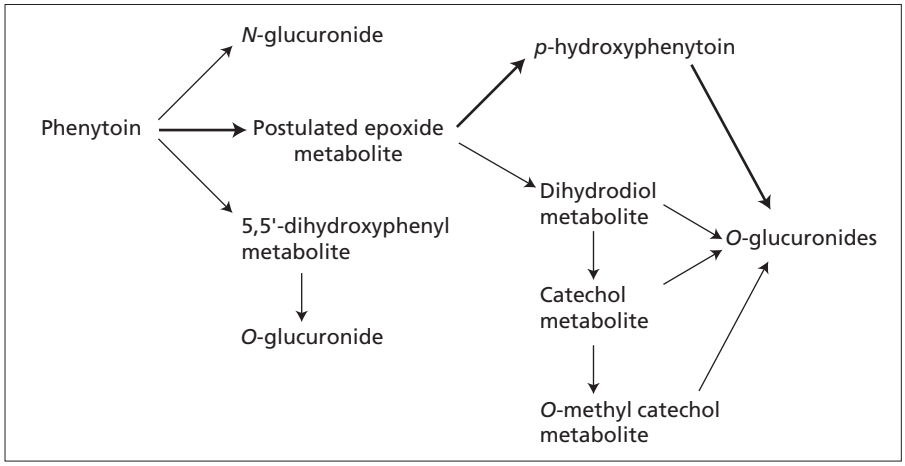

Fig. 47.2 Known metabolic pathways for phenytoin.

phenytoin in humans, the [S]-isomer being formed preferentially. The [R]-isomer of *p*-hydroxyphenytoin is formed via activity of CYP2C19. The glucuronide conjugate of the [S]-isomer of *p*-hydroxyphenytoin constitutes 75–95% of the total phenytoin metabolites in human urine. Neither *p*-hydroxyphenytoin isomer possesses known biological activity, or is likely to achieve a high enough concentration in the serum of patients with intact renal function to exert feedback inhibition on phenytoin biotransformation. There are suggestions that the postulated arene oxide intermediate and also postulated epoxide products of phenytoin metabolism may interact with various tissue proteins, leading to some idiosyncratic effects of the drug. Poor metabolizers of mephenytoin (methoin) form relatively little [R]-*p*-hydroxyphenytoin [20]. About 1 in 500 of the Japanese population is a slow hydroxylator of phenytoin [21], and hereditary poor metabolizers of the drug occur in other populations, related mainly to CYP2C9 and CYP2C19 functional polymorphisms. Various minor metabolites of phenytoin are known (Fig. 47.2), mostly additional derivatives of the arene oxide pathway, for example *m*-hydroxyphenytoin (possibly an analytical artefact), dihydrodiol, catechol, *O*-methyl catechol derivatives, and a molecule para-hydroxylated on each aromatic ring. A possible hydantoin ring-opened product and a *N*-glucuronide conjugate of the drug have also been described. Dickinson *et al.* [22] showed that, early in the course of repeated administration, there can be a degree of self-limited autoinduction of phenytoin metabolism, via the *p*-hydroxyphenytoin pathway and involving CYP2C19 more than CYP2C9.

Unlike most drugs, at clinical dosages phenytoin exhibits Michaelis–Menten rather than linear kinetics. The Michaelis constant of phenytoin is around 6 mg/L (24 μmol), lower than the usual serum concentration occurring clinically. Half-lives and clearances can be calculated for phenytoin, but the values are not constant in the individual, varying with the phenytoin concentration range over which they have been measured. The half-life is longer, and the clearance lower, at higher serum drug concentrations than at lower ones. The occurrence of Michaelis–Menten kinetics results in a non-linear relationship beteween serum phenytoin concentration and dose, with small dose increments

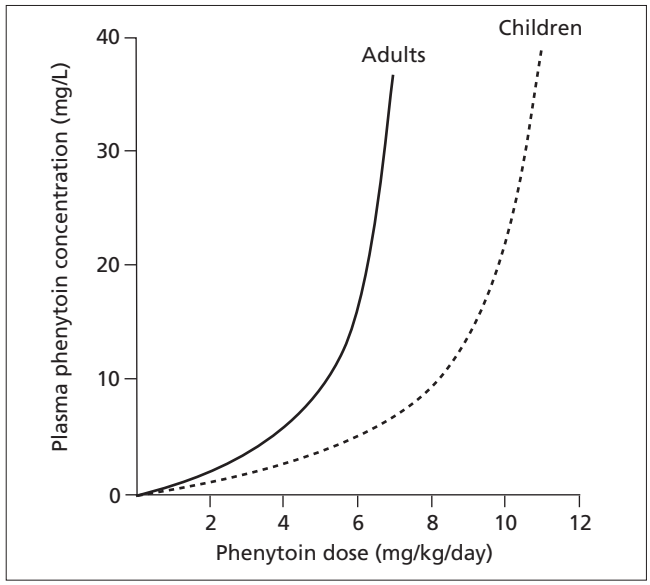

Fig. 47.3 Plot of mean steady-state plasma phenytoin concentration against dose in 21 adults and in 15 children younger than 15 years, generated from the data of ref. 69 (mean K_m for adults 5.8 mg/L and for children 5.3 mg/L; mean V_{max} for adults 8.1 mg/kg/day, and for children 12.5 mg/kg/day).

causing disproportionately large increases in serum concentrations. Typical dose–concentration curves in the individual are shown in Fig. 47.3. A representative published value for the drug's half-life over the concentration range likely to be encountered in human therapeutics is 22 ± 9 h, with a clearance value for adults of 0.02 L/kg/h, and for children below 5 years of age of 0.06 L/kg/h. Most published values of the K_m have been in the range of 3–30 mg/L, with the mean around 6 mg/L (24 μmol). The maximum velocity of phenytoin elimination (V_{max}) has been in the range 6–16 mg/kg/day, and is higher in young children than in adults [23].

The pharmacokinetic parameters of phenytoin are summarized in the table on pp. 605–606.

Drug interactions

Numerous interactions between phenytoin and endogenous substances and co-administered drugs have been reported [24–26]. A few of these interactions are pharmacodynamic in nature, mainly involving additional sedative effects when other drugs with sedative properties are also taken, and hoped for enhanced antiseizure effects when another AED is added to therapy. The great majority of phenytoin's interactions are pharmacokinetic and almost all involve altered rates of metabolism of one or both drugs (see Tables 47.1 to 47.3). The individual interactions that have been described are now too numerous for detailed discussion in this chapter. The outcomes of many of them are listed in Table 47.3. Their possible mechanisms are discussed below, though some of the interactions have unknown or uncertain mechanisms. Some interactions occur inconsistently, possibly because they involve multiple mechanisms which produce mutually antagonistic effects. The final outcome of a given interaction can be the sum of two opposing processes, each of which may vary from person to person, and also vary in extent depending on the concentrations of the interacting substances.

Table 47.1 Interactions which alter phenytoin absorption.

Substances which may decrease the oral bioavailability of phenytoin
Antacids
Calcium sulphate (within phenytoin capsules)
Charcoal (activated)
Protein hydrolysates for enteric feeding
Sucralfate
Theophylline

Table 47.2 Interactions which alter phenytoin distribution.

Substances causing phenytoin displacement from plasma protein binding sites
Acetazolamide
Ceftriaxone
Diazoxide
Heparin
Ibuprofen
Nafacillin
Oxacillin
Primidone
Salicylates
Sulphamethoxazole
Tolbutamide
Valproic acid

Interactions affecting phenytoin absorption

Examples of interactions affecting phenytoin absorption (Table 47.1) include the interaction between phenytoin and the calcium sulphate excipient which led to an Australasian outbreak of phenytoin intoxication and to that excipient being replaced by lactose. When phenytoin in solution is given via a gastrointestinal feeding tube at more or less the same time as certain protein hydrolysates used to provide enteral nutrition, the drug seems not to be fully absorbed. Studies in volunteers have sometimes failed to reproduce this effect, and have also failed to elucidate its chemical mechanism. It has been found that the problem can be avoided by administering the drug to patients several hours before, or after, the protein hydrolysate. Certain antacids, for example aluminium hydroxide, sucralfate and activated charcoal, are also reported to impair oral phenytoin absorption.

Interactions affecting phenytoin distribution

Certain endogenous substances and various acidic drugs (e.g. salicylates, valproic acid, heparin) displace phenytoin from its plasma protein binding sites (Table 47.2). *In vivo*, these potential interactions are unlikely to be of clinical importance in most instances, because the displaced drug is cleared more rapidly and the overall result of the interaction is usually a decrease in total drug concentration without any significant change in the concentration of unbound, pharmacologically active drug. However, these interactions must taken into consideration when total plasma phenytoin concentrations are used as a guide to dosage

Table 47.3 Metabolic interactions involving phenytoin. The level of evidence for these interactions varies across substances, and not all potential interactions occur consistently in all subjects.

Interacting substances causing raised phenytoin concentrations

Allopurinol, amiodarone[a], amphotericin, azapropazone[a], brivaracetam, bupropion, carbamazepine[b], chloramphenicol, chlordiazepoxide, chlorpromazine, cimetidine[b], clinafloxacin, clobazam, clofibrate, co-trimoxazole[a], dexamethasone, dextropropoxyphene[a], diazepam[b], dicoumarol, diltiazem, disulfiram, erythromycin, ethanol (acute intake), ethosuximide, famotidine, felbamate[b], fluconazole[a], flucytosine, 5-fluorouracil, fluvoxamine[a,b], fluoxetine[b], halothane, 10-hydroxyoxcarbazepine, imipramine[b], isoniazid[a], itraconazole, ketoconazole[b], losartan[a], methsuximide, methoin[b], methylphenidate, methylphenobarbital[b], metronidazole[a], miconidazole[a], nafimidone, nifedipine, nor-diazepam[b], omeprazole[b], paroxetine[a], phenylacetylurea, pheneturide, phenylbutazone[a], phenyramidol, pindolol, prochlorperazine, progabide, proguanyl[b], propoxyphene, propranolol[b], ranitidine, remacemide, sertraline[a], stiripentol[a], sulphaphenazole[a], sulthiame, tacrolimus, thioridazine, ticlopidine[a,b], tolbutamide[a], topiramate[b], torsemide[a], trazodone, trimethoprim[a], troxidone, valproic acid, verapamil, viloxazine, voriconazole, [*S*]-warfarin[a]

Interacting substances causing lowered phenytoin concentrations

Aciclovir, aspirin, bleomycin, carbamazepine[d], carmustine, ciprofloxacin, cisplatin, dexamethasone, diazepam, diazoxide, dichloralphenazone, doxycycline, evening primrose oil, ethanol (chronic intake), folate, methotrexate, nelfinavir, nitrofurantoin, oxacillin, phenobarbital, pyridoxine, reserpine, rifampicin[c,d], salicylates, theophylline, tolbutamide, vigabatrin, vinblastine

Phenytoin causing raised concentrations of other substances

Chloramphenicol, phenobarbital, tirilazad, warfarin

Phenytoin causing lowered concentrations of other substances

Albendazole, antipyrine, atorvastatin, bromphenac, campothecin, carisbamate, carbamazepine, chloramphenicol, cisactracurium, clobazam, clonazepam, clozapine, ciclosporin, cyclophosphamide, dexamethasone, dicoumarol, digoxin, disopyramide, doxycycline, efavirenz, ethosuximide, felbamate, felodipine, flunarazine, haloperidol, 10-hydroxycarbazepine, irinotecan, itraconazole, lamotrigine, lidocaine, losartan, methadone, methotrexate, metyrapone, mexiletine, midazolam, mirtazepine, misonidazole, nimodipine, nisoldipine, nortriptyline, oral contraceptives, oxazepam, paracetamol, pethidine, phenobarbital, prednisolone, primidone, praziquantel, quetiapine, quinidine, retigabine, all-*trans*- and ±-*cis*-retinoic acid, simvastatin, sirolimus, tacrolimus, taxanes, teniposide, theophylline, thiotepa, tirilazad, topiramate, topotecan, tricyclic antidepressants, valproic acid, vecuronium, vinca alkaloids, voriconazole, warfarin, zonisamide

Data from refs 28–30 and miscellaneous sources. [a]known substrate and/or inhibitor of CYP2C9; [b]known inhibitor and/or substrate of CYP2C19; [c]known inducer of CYP2C9; [d]known inducer of CYP2C19.

adjustments. In fact, in the presence of an increased unbound fraction, as may occur in the presence of a displacing agent, therapeutic and toxic effects will occur at total phenytoin concentrations that are lower than usual.

Interactions altering phenytoin metabolism

Phenytoin is eliminated from the body mainly by virtue of CYP2C9- and CYP2C19-catalysed oxidations to *p*-hydroxyphenytoin (Table 47.3). Co-administered drugs which induce the activity of either or both of these CYP isoenzymes are likely to cause increased phenytoin elimination, and hence lowered serum concentrations of the drug. Conversely, drugs which competitively inhibit either or both of these CYP isoforms tend to raise serum phenytoin concentrations. Despite these known interaction mechanisms, the metabolic basis of many of the interactions involving altered phenytoin concentrations remains uncertain.

Inhibition of phenytoin metabolism occurs with the CYP2C9 substrates/inhibitors sulphaphenazole, phenylbutazole, fluconazole, azapropazone, disulfiram, metronidazole and stiripentol, and with the CYP2C19 substrates/inhibitors felbamate, omeprazole, cimetidine, fluoxetine and imipramine. Ethosuximide, felbamate, methsuximide, oxcarbazepine or sulthiame may also increase serum phenytoin levels. Because of the Michaelis–Menten elimination kinetics of phenytoin, a small degree of inhibition of the drug's metabolism can produce a disproportionately large increase in serum phenytoin concentrations and possibly drug toxicity.

Interactions involving induction of the drug's metabolism, which reduce its serum concentrations, are far less common and are more likely to go unnoticed, unless serum phenytoin concentrations are monitored, or seizure control deteriorates. Serum phenytoin levels often decrease when primidone, vigabatrin, carbamazepine or phenobarbital is added as co-medication, though sometimes the opposite effect occurs if carbamazepine or phenobarbital is added. The effects of valproic acid on serum phenytoin levels vary. Valproic acid, in fact, may inhibit phenytoin metabolism, and this mechanism may cause an increase in plasma unbound phenytoin concentration. Because at the same time valproic acid displaces phenytoin from plasma protein binding sites, however, the total plasma phenytoin concentration may show little change, or may even be decreased.

Phenytoin affecting other substances

Phenytoin can alter the body's elimination of other substances by (a) inducing the synthesis of the CYP isoenzymes responsible for their metabolism, not only CYP2C isoforms but also CYP3A4 (which catalyses the oxidation of many drugs) and CYP1A1/2, and also by inducing the synthesis of certain glucuronyl transferases involved in drug conjugation; or (b) serving as a competitive inhibitor of the metabolism of other CYP2C9 or CYP2C19 eliminated drugs. It is not yet known how important other mechanisms are. As mentioned above, both induction and inhibition can occur simultaneously, with clinical effects that are difficult to predict.

In most situations, the consequences of enzyme induction prevail. As a result, the concentrations of carbamazepine, clobazam, clonazepam, felbamate, lamotrigine, primidone, tiagabine, topiramate, valproic acid, ethosuximide and zonisamide can fall when phenytoin is added as co-medication. The effect of phenytoin on phenobarbital concentrations varies, with levels rising or falling. By causing enzyme induction, phenytoin can also decrease the serum levels and clinical effectiveness of many cardiovascular

agents, chemotherapeutic agents, hormonal agents, psychotropic agents and many other substances (Table 47.3).

Serum level monitoring

Within limits, increasing phenytoin doses and the consequent increases in serum phenytoin concentrations correlate with increasing degrees of seizure control in types of epilepsy responsive to the drug. Since the publications of Kutt *et al*. in 1964 [27], it has become widely accepted that serum phenytoin concentrations in the range of 10–20 mg/L (40–80 μmol) are usually associated with the best chance of achieving seizure control without producing drug overdosage manifestations. This concentration range is usually considered the 'therapeutic' or 'target' range for the drug. However, certain authors (e.g. Loiseau [28]) have set the lower limit of the range at around 7 mg/L (28 μmol), and the upper limit at 25 mg/L (100 μmol). Everyday clinical experience suggests that these wider limits are valid, and that some patients may even do best at concentrations higher or lower than this range [29].

There is evidence that generalized tonic–clonic seizures may be fully controlled once serum phenytoin levels exceed 6–8 mg/L, but much higher levels may be needed for partial seizure control. Schmidt *et al*. [30] found that a mean serum phenytoin concentration of 14 mg/L (56 μmol) was associated with control of generalized tonic–clonic seizures, but a mean concentration of 23 mg/L (92 μmol) was needed for control of partial seizures. The therapeutic range values for the drug in plasma water (unbound plasma concentration) or saliva are approximately one-tenth of those in whole plasma (serum). In theory, it would be better always to measure the drug's concentration in plasma water, as this would obviate the effects of variation in the plasma protein binding of the drug in disease, in certain physiological states and in the presence of displacing co-medications. In practice, the unbound (free) drug concentrations are more expensive to measure, and less accurate. They are rarely needed unless there is good reason to suspect altered plasma protein binding of the drug.

In practice, with serum phenytoin concentrations in the so-called 'therapeutic' or 'target' range of 10–20 mg/L (40–80 μmol), new steady-state conditions should apply 4–8 days after a phenytoin dosage change, though at higher concentrations the period required to reach steady state may be longer (up to about 2 weeks). Under steady-state conditions in the therapeutic drug concentration range, the peak-to-trough fluctuation in serum phenytoin concentration in adults is likely to be of the order of ± 10% over a 12-h dosage interval, but greater fluctuations occur in children. At lower phenytoin concentrations, under steady-state conditions, the interdosage fluctuations are also likely to be proportionately wider.

There are wide interindividual variations in steady-state serum phenytoin concentrations at conventional doses of the drug (300 or 400 mg/day), and an appreciable proportion of the values fall outside the therapeutic range. The correlation between dose and level is better if phenytoin dosage is expressed relative to body weight. As already mentioned, the maximum velocity of phenytoin biotransformation (or the clearance value) is higher in children than in adults [23]. A daily phenytoin dose of 5 mg/kg will yield a mean mid-therapeutic range steady-state serum phenytoin concentration of 15 mg/L (60 μmol) in adults. However, prepubertal children will need a mean daily phenytoin dose of 11 mg/kg to achieve a similar mean serum drug concentration. The mean dose required is lower in neonates and in children in the first few months of life. It also tends to be slightly lower in the elderly than in younger adults.

The pregnant woman's capacity to eliminate phenytoin begins to increase progressively after the first few weeks of pregnancy so that serum phenytoin concentrations, relative to drug dose, begin to fall [31]. The drug concentration returns to prepregnancy values over a few weeks after childbirth, if the drug dosage remains unchanged. This sequence of changes needs to be kept in mind if it is considered desirable to maintain serum phenytoin concentrations at their prepregnancy values throughout pregnancy, and afterwards. However, if this is done, the reduced serum protein binding of the drug in the third trimester of pregnancy should be taken into consideration. The altered disposition of the drug during pregnancy appears to be a consequence of increased drug metabolism. When Michaelis–Menten parameters of phenytoin during pregnancy were determined after intravenous administration of stable isotope-labelled drug, and compared with those determined after parturition in the same women, Dickinson *et al*. [32] found that mean V_{max} was significantly higher during pregnancy than post partum (1170 ± 600 mg/day versus 780 ± 470 mg/day). Likewise, K_m was also higher during pregnancy than post partum, for values calculated both in whole plasma (18.2 ± 8.4 versus 10.2 ± 7.4 mg/L) and in plasma water (2.50 ± 0.85 mg/L versus 1.16 ± 0.65 mg/L), the latter change being statistically significant. There may also be a premenstrual and menstrual fall in serum (and saliva) phenytoin concentrations in some women. This may correlate with the occurrence of breakthrough seizures, that is catamenial epilepsy.

In clinical practice, a patient's initial or continuing phenytoin dosage may have to be adjusted to achieve a steady-state serum phenytoin concentration within a desired range. Because of the Michaelis–Menten elimination kinetics of the drug, steady-state serum phenytoin concentrations will increase out of proportion to the relative size of an increase in phenytoin dosage [33] (Fig. 47.3). Failure to realize this, and prescribing phenytoin dosage increments in the expectation that the drug's serum concentrations and effects will increase in proportion to the dosage increase, often results in phenytoin intoxication. This phenomenon makes phenytoin dosage adjustment hazardous in the hands of the uninformed.

In patients with severe liver and renal disease, the reduced serum protein binding capacity for phenytoin needs to be taken into consideration when interpreting total serum phenytoin concentrations. In such circumstances, measurement of unbound serum phenytoin, or salivary phenytoin concentrations, is likely to provide more reliable information. There may be a temporary fall in serum phenytoin levels in the 24 h after craniotomy.

Efficacy

Merritt and Putnam [34] first demonstrated in 1938 the efficacy of phenytoin against major seizures in the more common epilep-

Table 47.4 Details of published studies comparing phenytoin with other antiepileptic drugs (AEDs) in monotherapy.

Drug compared	Author	Number of studies	Patients studied	Seizure disorder		Outcome
				Generalized tonic–clonic	Partial	
Phenobarbital	Taylor [55][a]	4	599	Yes	Yes	No difference; phenobarbital more likely to be withdrawn
	Painter [61]	1	59	Neonatal seizures	Drugs equally but incompletely effective	
Carbamazepine	Tudur Smith [56][a]	3	551	Yes	Yes	No difference
	Callaghan [62]	1	117	Yes	Yes	Phenytoin more effective for generalized tonic–clonic seizures
	Thilotammal [63]	1	103	Yes – children		No difference; more frequent side-effects with phenytoin
Oxcarbazepine	Muller [57][a]	2	480	Primary generalized	Yes	No difference for generalized seizures; oxcarbazepine better for time to withdrawal in partial seizures
Valproic acid	Tudur Smith [58][a]	5	669	Primary generalized	Yes	No difference for generalized seizures; no result for partial seizures
	Shakir [64]	1	33	Epilepsy		Reasonably similar efficacies
	Wilder [65]	1	87	Yes	Yes	No difference
	Callaghan [62]	1	122	Yes	Yes	No difference
	Thilotammal [63]	1	100	Yes – children		No difference
	Beenen [66]	1	100	Post-craniotomy prophylaxis		No difference
Lamotrigine	Steiner [67]	1	181	Yes	Yes	No difference
Clobazam	Canadian Study Group [68]	1	76	Yes – resistant cases	Yes – resistant cases	No difference in efficacy
Magnesium sulphate	Duley [59][a]	6	897	Eclampsia		Magnesium sulphate substantially better

No difference: no statistically significant difference.

[a] Cochrane Collaboration study reanalysing appropriate published material for which original data were available (number of studies included in each analysis is shown in the next column). None of the Cochrane Collaboration analysed material is included in the other studies cited.

tic syndromes. They gave the drug for 2–11 months to 142 patients with seizure disorders not controlled by phenobarbital and bromides. Bromides were withdrawn but phenobarbital was continued and phenytoin commenced. In 118 patients with frequent 'grand mal' seizures, 'complete relief' was obtained in 58%, with a 'marked decrease' in seizures in another 32%. The corresponding figures for 74 patients with 'petit mal' (some of whom would now be classified as having complex partial seizures) were 35% and 49% respectively, and for the six with 'psychomotor seizures', 67% and 33%. By modern standards, the study design was rather inadequate. The follow-up was short, background therapy varied between patients, there was no placebo-treated control group, and seizure disorder classification sometimes appeared uncertain. Nonetheless, the study's conclusions were borne out in subsequent routine practice and later clinical investigations. Thus, in newly diagnosed cases of generalized convulsive or partial epilepsy, Shorvon *et al*. [35] found that after 2 years of phenytoin monotherapy there was 78% full seizure control.

Several publications are now available that review the efficacy of phenytoin relative to other, mainly newer, AEDs used in monotherapy in patients with epilepsy, including two studies [36,37] and five Cochrane reviews [38–42]. Table 47.4 summarizes the nature of the material studied and the outcomes of the Cochrane reviews and certain other relevant studies in which the methodology may not have been identical with the Cochrane reviews, but which do add further information. Basically, for varieties of frequently occurring epileptic disorders expected to be responsive to phenytoin, the efficacy and tolerability of the drug seems not to differ appreciably from that of other commonly used and usually more expensive contemporary AEDs.

In addition to showing efficacy in patients with generalized tonic–clonic seizures and partial seizures, phenytoin has been found to be useful in the prevention of acute symptomatic seizures shortly after craniotomy or traumatic brain injury [43]. However, it is ineffective in preventing the occurrence of late seizures or the development of post-craniotomy or post-traumatic epilepsy in these patients [43,44]. Experience has also established that phenytoin is ineffective for treating myoclonic seizures (irrespective of their age of onset), absence and atonic seizures of primary generalized epilepsy, infantile spasms and seizures in the Lennox–Gastaut syndrome. The drug has also proved ineffective in two reasonably common varieties of situation-related seizures, namely

febrile convulsions of infancy and eclamptic seizures of pregnancy toxaemia.

Intravenous phenytoin has been successful in treating neonatal seizures and convulsive status epilepticus. These indications are discussed in Chapters 13 and 18, respectively.

Adverse effects

Phenytoin has been widely used for nearly 70 years, and numerous adverse effects of the drug are known (Table 47.5). Some of these are clearly related to the drug's concentration in the body, many representing what would be regarded as overdosage effects. Some unwanted effects are hypersensitivity reactions, possibly related to immune-mediated interactions involving chemical adducts formed between various tissue proteins, for instance liver microsomal membrane proteins [45], and the postulated arene oxide intermediate derivative of phenytoin hydroxylation, or the drug's catechol metabolite. Adduct formation itself may also alter the composition of various body tissue elements and produce structural change in tissues. However, the mechanisms of some unwanted effects are currently unexplained. The common or otherwise important reported adverse effects of phenytoin are listed in Table 47.5.

Effects on the nervous system

Phenytoin overdosage tends to produce vestibulo-cerebellar disturbances. The earliest manifestation may be a horizontal nystagmus which typically occurs at serum concentrations above 20 mg/L (80 μmol). At concentrations above 30 mg/L (120 μmol) ataxia of gait and double vision occur, and at concentrations above 40 mg/L (160 μmol) drowsiness, sometimes with nausea and vomiting [27]. Coma develops if the drug concentration becomes high enough. However, there are large individual differences, and in some patients unwanted effects occur at serum levels above or below the usual optimal range. Conversely, in other patients, adverse effects may be absent at levels above 30 mg/L (120 μmol).

Dizziness and headache are additional possible adverse effects of phenytoin therapy. Occasional patients may experience mood disorders, mainly depression, as the dose of the drug is increased, but the risk of depression is small. At therapeutic concentrations, phenytoin has been reported to decrease performance in various tests of cognitive function. However, this has been only inconsistently demonstrated, and may be partly an artefact of the drug's interference with motor coordination [46]. Despite the earlier suggestion that carbamazepine caused less interference with cognitive function than phenytoin, the literature review of Kalviainen *et al*. [47] suggested that, at therapeutic concentrations, there was little real difference between the two drugs in this regard.

Seizure control may worsen in some patients as serum levels of phenytoin become 'supratherapeutic', or when phenytoin is prescribed inappropriately in syndromes known to be associated with absence or myoclonic seizures.

Occasionally, phenytoin overdosage results in various dyskinetic and dystonic involuntary movements, asterixis or ophthalmoplegia. There are also reports of the drug causing subclinical and occasionally overt peripheral neuropathy. Shorvon and Reynolds [48] found mild abnormalities of peripheral nerve conduction in 18% of a series of patients (with non-toxic phenytoin levels) who had no clinically detectable evidence of peripheral neuropathy. At toxic levels, a more severe reversible demyelinating neuropathy may occur.

Phenytoin overdosage may cause decreased colour vision discrimination. Cerebellar atrophy has been reported in persons with long-standing phenytoin overdosage [49]. In one individual, cerebellar atrophy was reported after a severe acute phenytoin overdose.

Table 47.5 More common and/or more serious adverse effects of phenytoin.

Nervous system	Nystagmus, gait ataxia, diplopia, dyskinesias, dizziness, headache, mood and cognitive changes, sedation, diplopia, depressed consciousness, cerebellar degeneration
Skin	Morbilliform rash in 5–10%, Stevens–Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hirsutism, acne
Gums	Hypertrophy
Bone	Osteomalacia
Haematological	Lymphadenopathy (pseudolymphoma), megaloblastic anaemia, suppression of individual blood cell lines
Other hypersensitivity reactions	Aromatic anticonvulsant hypersensitivity syndrome, systemic lupus erythematosus
Cardiovascular	Cardiac conduction defects, arrhythmias, hypotension (intravenous therapy), cardiac depression
Biochemical alterations	Increased: γ-glutamyl transpeptidase, alkaline phosphatase, sex hormone-binding globulin Reduced: folate, thyroid hormones, sex hormones
Teratogenesis	Various malformations – the risk is moderately raised in monotherapy but is higher if other antiepileptic drugs are co-administered Fetal hydantoin syndrome (?)

Effects on the skin

Some 5–10% of patients given phenytoin develop a measles-like rash which usually first appears on the trunk, mostly in the second week of drug intake. If treatment with the drug is not ceased at that stage, more extensive skin and internal organ involvement can develop. Other cutaneous reactions, for example Stevens–Johnson syndrome, systemic lupus erythematosus, exfoliative dermatitis and toxic epidermal necrolysis, are less common. The incidence of phenytoin-related rashes appears to be higher in patients who developed rashes from other aromatic AEDs and in those receiving radiotherapy for intracranial tumours [50]. Phenytoin should be discontinued immediately if a rash appears.

The typical acute phenytoin morbilliform rash described above may merge into the various expressions of the aromatic anticonvulsant hypersensitivity syndrome. In this condition the rash becomes more extensive whilst remaining erythematous, mucosal involvement with ulceration may develop, skin exfoliation may occur and eosinophilia, hepatitis and other evidence of systemic organ involvement may appear. Cross-sensitivity with other drugs is common, and 60% of affected persons experience similar

reactions if subsequently exposed to carbamazepine or phenobarbital. The syndrome is thought to depend on an autoimmune response to adducts formed between phenytoin metabolites and various tissue protein components (e.g. microsomal proteins) [45].

Phenytoin may cause an overgrowth of body hair, particularly in dark-haired females, acne and coarsening of facial features. These effects can be cosmetically important.

Intravenous administration of phenytoin may lead to a 'purple glove' syndrome involving the hand and forearm distal to the administration site, with local progressive skin discoloration, oedema and pain. This phenomenon occurred in 5.9% of one series of 152 patients given the drug intravenously [51], although clinical experience suggests a much lower rate. Thrombophlebitis may develop in the vein into which the drug has been administered. The incidence of these adverse effects appears to be lower when intravenous fosphenytoin is used in place of phenytoin [15].

Effects on the gums

The association between gum hyperplasia and phenytoin intake has long been recognized. The subject has been reviewed on a number of occasions [52]. Estimates of frequency have varied between 13% and 40%. Most authors have noted a correlation between the degree of gum hyperplasia and the serum phenytoin level. Poor dental hygiene makes the hypertrophy more noticeable. The causal mechanisms are unclear. Reduced immunoglobulin A (IgA) concentrations in saliva were originally considered relevant. More recently, the recognition that phenytoin is metabolized in gum tissue to *p*-hydroxyphenytoin has led to the hypothesis that the resulting arene oxide metabolic intermediate forms adducts with various tissue proteins in the gums, leading to gum overgrowth. However, the degree of gum hypertrophy seemed unrelated to the salivary *p*-hydroxyphenytoin concentration [53]. Serum concentrations of basic fibroblast growth factor increase in the presence of phenytoin intake, and these concentrations seem to correlate with the degree of gum hyperplasia [54].

Effects on bone

Patients receiving long-term phenytoin therapy, with or without other older AEDs, can develop reduced bone mineral densities and overt osteomalacia related to increased bone turnover. Serum calcium levels may fall and alkaline phosphatase levels rise. Serum 25-hydroxycholecalciferol concentrations are reduced. The risk of osteomalacia is highest in circumstances where diet is poor in vitamin D content and there is little exposure to sunlight. Osteomalacia is probably due to induction of vitamin D metabolism and possibly impaired intestinal absorption of dietary calcium.

Effects on lymphoid tissue

Rarely, chronic phenytoin intake has been associated with the development of widespread lymphadenopathy which disappears when intake of the drug is ceased. The histological appearance of the affected lymph glands is reminiscent of that of Hodgkin's disease, and the entity is referred to as a pseudolymphoma syndrome. Even more uncommonly, instances of true lymphoma have been reported in association with phenytoin intake.

Effects on folates

Phenytoin intake causes a reduction in serum and red blood cell folate levels. The mechanisms of this effect have not been fully elucidated. The extent of the reduction is proportional to the serum phenytoin concentration. There have been suggestions that this fall in folate concentration plays a role in the slowing of intellectual performance. Folate deficiency occasionally results in megaloblastic anaemia in patients receiving long-term phenytoin therapy.

Cardiovascular effects

Oral phenytoin therapy in usual dosages very rarely causes cardiovascular disturbances. Intravenous administration of phenytoin is potentially hazardous, especially if the rate of administration exceeds 50 mg/min in adults or 1–3 mg/min/kg in children, or if the dose exceeds the recommended levels. Hypotension, cardiovascular collapse and central nervous system depression can then occur. Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Hypotension usually occurs when the intravenous drug is administered rapidly. However, even at slower infusion rates, problems occasionally arise. Severe cardiovascular complications are more common in elderly or gravely ill patients.

Other effects

Phenytoin intake can precipitate attacks of porphyria in sufferers from the disorder.

If the nature of paroxysmal hypoglycaemic symptoms is unrecognized and these symptoms are misdiagnosed as epileptic in nature, prescription of phenytoin can delay the diagnosis of an insulinoma, since phenytoin can diminish pancreatic insulin secretion.

Rarely, phenytoin has caused hepatitis, vasculitis, interstitial lung infiltration, interstitial nephritis, myopathy, thyroiditis, arthritis and the suppression of the formation of particular lines of blood cell. The teratogenic effects of phenytoin are discussed below.

Phenytoin intake can produce a range of biochemical effects, which are often asymptomatic. They include raised serum or plasma levels of γ-glutamyl transpeptidase, alkaline phosphatase, high-density lipoprotein (HDL) cholesterol, caeruloplasmin, copper, prolactin and sex hormone-binding globulin. Phenytoin use has also been associated with reduced serum concentrations of folate (discussed above), IgA, IgG, IgE, IgM, fibrinogen, thyroxine, tri-iodothyronine (but not free T_4 and T_3), protein-bound iodine, vitamin K, vitamin E, vitamin D metabolites (mentioned above), cortisol, oestrogens, progesterone, free testosterone, pyridoxal phosphate, tryptophan and thiamine. The disturbances affecting sex hormone metabolism may result in reduced libido and other sexual disturbances.

In the neonate exposed to phenytoin during pregnancy, blood coagulation defects, probably due to a relative deficiency of vitamin K-catalysed clotting factors, may cause bleeding on the fifth neonatal day unless the mother receives vitamin K before delivery and/or the baby receives prophylactic vitamin K immediately after birth. Presumably phenytoin induces the metabolism of the vitamin to inactive derivatives.

Teratogenicity

For almost 40 years, since the publication of Meadow [55], it has been known that there is an approximate doubling or trebling in the rate of malformed infants born to pregnant women taking AEDs, including phenytoin. The role of phenytoin has been difficult to interpret, because (1) the teratogenicity of AEDs has tended to be treated as a class effect; (2) a distinction has not been made between phenytoin used as monotherapy and when combined with other AEDs (the fetal malformation risk is higher with polytherapy exposure) and (3) optimal control data collected simultaneously and in a similar manner to the phenytoin-exposed pregnancies have not been obtained.

In addition to comprehensive reviews of AED teratogenesis [56], there are now several published studies reporting fetal malformation rate data for pregnancies exposed to phenytoin monotherapy. In five of these, the treated and control pregnancies were collected and evaluated simultaneously and similarly. These five studies have involved 390 phenytoin-treated and 676 AED-unexposed control pregnancies in women with epilepsy. The relative risk of fetal malformations has ranged between 1.0 and 3.0, and the increase was not statistically significant in any individual series. Malformation rates in the five series ranged between 2.4% and 16.0% in the phenytoin-exposed pregnancies and between 0.8% and 5.3% in the controls [57].

Various phenytoin-associated malformations have been reported. The more severe include facial clefts, diaphragmatic hernias, hip dysplasias and congenital heart abnormalities. A 'fetal hydantoin' syndrome has been described [58], involving what is claimed to be a characteristic facies with wide-spaced eyes, together with deformities of the fingernails, slender and shortened terminal phalanges, mild mental retardation and poor infantile growth and development. Many of these minor abnormalities become unrecognizable within the first few years of life. Partial rather than full syndromes are more common. There is some controversy in the literature as to whether or not the fetal hydantoin syndrome is a genuine entity and, if it is, whether or not it is specific to fetal exposure to phenytoin in pregnancy, or is also associated with exposure to other AEDs.

A good deal of experimental embryological work has been undertaken to explore the mechanisms of phenytoin-associated fetal malformations. Fetal maldevelopment may possibly result from reactive phenytoin metabolic free radical intermediates, for example arene oxide derivatives, which form adducts with fetal tissue proteins. If they are not inactivated by glutathione [59], free radical intermediates produced by the activity of tissue peroxidases which metabolize phenytoin to hydroxyl radicals may oxidize various fetal macromolecules. Arene oxide adducts would be more likely to occur at higher concentrations if the activity of the enzyme epoxide hydrolase (which catalyses the further metabolism of arene oxides and epoxides) was deficient. There is evidence that low levels of the enzyme epoxide hydrolase in amniocytes and fetal fibroblasts were associated with the fetal hydantoin syndrome. It has also been proposed that phenytoin-induced bradycardia may make the embryo hypoxic [60] and cause the formation of toxic reactive oxygen species [61]. *p*-Hydroxyphenytoin itself may be embryotoxic [62].

Overall, it seems likely that intrauterine phenytoin exposure may cause fetal malformations, but the risk is not high if phenytoin is taken as monotherapy. Phenytoin appears less likely to cause serious spinal malformations than carbamazepine or valproic acid. The comparative teratogenic risks of available AEDs are discussed in greater detail in Chapter 25.

Place in current therapy

The studies discussed above provide consistent evidence that phenytoin is as effective as other widely used established AEDs in suppressing seizures in common varieties of epilepsy. Its adverse effect profile, and its ease of use, may differ in some ways from other agents with established similar antiepileptic efficacy. A consensus appears to have emerged, at least in Europe, that carbamazepine or a newer generation AED is preferable to phenytoin for the first-line treatment of epilepsies with generalized tonic–clonic seizures, or with simple or complex partial seizures. This view is based on the superior tolerability profile of these drugs and greater ease of use (the latter probably in non-expert hands). Brodie and Kwan [63] attempted to make a comparison of AEDs in a quantitative basis by developing a simple scoring system involving a number of criteria (a 'star' system). Phenytoin scored less well than other AEDs, but the scientific basis for this scheme is arguable. Overall, phenytoin remains a satisfactory agent for treating patients with partial seizures, with or without secondary generalization, and patients with primary generalized tonic–clonic seizures. The choice of phenytoin has greater justification when the drug is used by those familiar with its pharmacokinetics and adverse effect profile. It also has the advantages of very low cost and of availability in parenteral formulations.

Phenytoin has also had some use in tic douloureux, certain cardiac arrhythmias, various neurogenic pain syndromes, as a prophylactic in occasional varieties of migraine, and in paroxysmal choreoathetosis and myotonia, though other agents are probably more efficient for many of these disorders. It is sometimes applied locally to promote skin healing.

A reasonable initial daily phenytoin dose is 5 mg/kg in adults, and 10 mg/kg in prepubertal children. These doses offer a good chance of obtaining a steady-state serum phenytoin concentration in the range of 10–20 mg/L (40–80 μmol) within 1 week, and are unlikely to cause overdosage effects. The full anticipated daily dose can be used from the commencement of therapy. Pharmacokinetic considerations suggest that once-daily intake should be satisfactory, and it often proves so in practice. However, twice-daily intake does not appear to increase compliance problems, and allows greater security against the consequences of missed doses. Twice-daily intake is often preferable in children, as the half-life of phenytoin is shorter in children than in adults.

The serum (or plasma) phenytoin concentration should be measured once there has been time for steady-state conditions to apply. If, in light of the measurement and clinical response, it appears clinically desirable to adjust the drug dose, the non-linear relationship between steady-state serum phenytoin concentrations and dosage should be kept in mind in determining the magnitude of the dose change. Nomograms have been devised in an attempt to predict precise phenytoin dosage adjustments needed to yield particular serum phenytoin concentrations. However, in practice, the size of the available dosage units

(generally 30, 50 and 100 mg) tends to determine the dosage adjustment that will be made. In most adults, a dose increment of 100 mg is unlikely to lead to overdosage manifestations if the patient's steady-state serum phenytoin concentration is below 10 mg/L (40 μmol), and a dose increment of 30 or 50 mg is likely to be tolerated if the serum phenytoin level is between 10 and 15 mg/L (40 and 60 μmol). In children, smaller-sized increments are necessary.

The therapeutic range of serum phenytoin concentrations is usually considered to be 10–20 mg/L (40–80 μmol). However, as mentioned earlier, some patients achieve seizure control at serum phenytoin concentrations as low as 7 mg/L (28 μmol) and even lower, whilst others require, and tolerate, levels of 25 mg/L (100 μmol) or higher before seizures cease. The latter is particularly the case for partial seizures, whilst in the same patient lower concentrations of the drug may allow control of tonic–clonic convulsive seizures [30]. In patients in whom the natural history of epilepsy is not known, or when it is expected that seizures will recur only at long intervals, it is reasonable to try to achieve an initial steady-state serum phenytoin concentration in the range of 7–20 mg/L (28–80 μmol). Thereafter, further dosage adjustment depends on the clinical response. In varieties of epilepsy in which seizures occur frequently from the outset, the clinical response provides the better guide to phenytoin dosage. Achieving serum phenytoin concentrations within the quoted therapeutic range guarantees neither the optimal possible control of seizures nor the absence of adverse effects. Once a satisfactory phenytoin dosage regimen has been achieved in a particular patient, it will rarely be necessary to alter that regimen over many years, unless non-compliance occurs, the epilepsy is associated with progressive brain disease, late-stage adverse effects of prolonged phenytoin intake occur, or another drug is prescribed which interacts with the phenytoin. Phenytoin dosage may need to be reduced in the presence of severe liver disease, though often not in the presence of renal failure. However, the reduced serum albumin concentrations in patients with severe liver or renal disease may confound the interpretation of serum phenytoin concentrations, and make measurement of the unbound drug concentration, or of salivary concentrations, desirable as a guide to therapy.

Intravenous phenytoin often provides effective therapy for convulsive status epilepticus. However, intravenous therapy carries a risk of cardiovascular complications, which is minimized by keeping the rate of administration below 50 mg/min in adults and 1–3 mg/min/kg in neonates or children. Even in patients not previously receiving phenytoin, a total loading dose of 20 mg/kg should not be exceeded. Continuous monitoring of the ECG and blood pressure is strongly recommended. The parenteral formulation of phenytoin should be injected slowly into a large vein, through a large-gauge needle or intravenous catheter. An injection of intravenous phenytoin should be followed by a 'flushing' injection of sterile saline through the same needle or catheter to avoid local venous irritation. Fosphenytoin may offer some advantages in minimizing the complications of intravenous therapy. Prolonged infusions of phenytoin should be avoided. Intravenous phenytoin therapy requires close medical supervision. The treatment of status epilepticus and acute seizures is dealt with in more detail in Chapter 18.

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48 Piracetam

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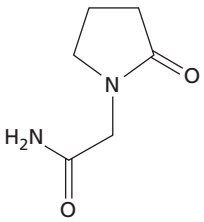

Primary indications	Monotherapy or adjunctive therapy for myoclonus
Usual preparations	Tablets or capsules: 400, 800, 1200 mg; solution: 20, 33%
Usual dosages	Initial: 7.2 g/day. Maintenance: up to 24–32 g/day
Dosing frequency	2–3 times/day
Significant drug interactions	None
Serum level monitoring	Not routinely done
Target range	Not applicable
Common/important adverse effects	Dizziness, insomnia, nausea, gastrointestinal discomfort, hyperkinesis, weight gain, tremulousness, agitation, drowsiness, rash
Main advantages	Well tolerated and very effective in some resistant cases
Main disadvantages	Not effective in many cases
Mechanisms of action	Unclear
Oral bioavailability	Close to 100%
Time to peak levels	30–40 min
Metabolism and excretion	Renal excretion without known metabolism
Volume of distribution	0.5–0.75 L/kg
Elimination half-life	4–5 h
Plasma clearance	–
Protein binding	None
Active metabolites	None
Comment	Useful drug for some patients with refractory myoclonus

Introduction

The pyrrolidone (2-oxo-pyrrolidine) derivatives are a family of compounds which have unique properties of potential value in various neurological settings [1]. Over 12 000 compounds in this chemical group have been synthesized in the past three decades, and over 900 compounds have undergone primary and secondary screening for anticonvulsant activity at UCB Pharma and other pharmaceutical companies. Experimental and clinical work on the pyrrolidones was focused initially on the so-called nootropic effect [1–3], then on potential neuroprotection after stroke, and most recently on their antiepileptic and antimyoclonic effects.

Piracetam was the first drug of the class to be developed, following pioneering research by Giurgea and Salama [2,3], working in the UCB laboratories. It was Giurgea who coined the term nootropic to mean (a) enhancement of learning and memory, (b) facilitation of cross-hemispheric information flow, (c) neuroprotection and (d) lack of other psychopharmacological actions (e.g. sedation, analgesia, or motor or behavioural changes). These effects distinguish this class of compounds from other psychoactive drugs. The clinical value of piracetam as a nootropic is contentious, and the findings are not considered conclusive enough currently to allow licensing for this indication in the USA or the UK. However, piracetam has been, and continues to be, widely used for this indication in many other countries, particularly in the developing world, with over 1 000 000 people worldwide reported to be receiving the drug. There are notable geographical differences in the use of this drug class, with expanding programmes of clinical studies particularly in Japan and Asia. Whilst

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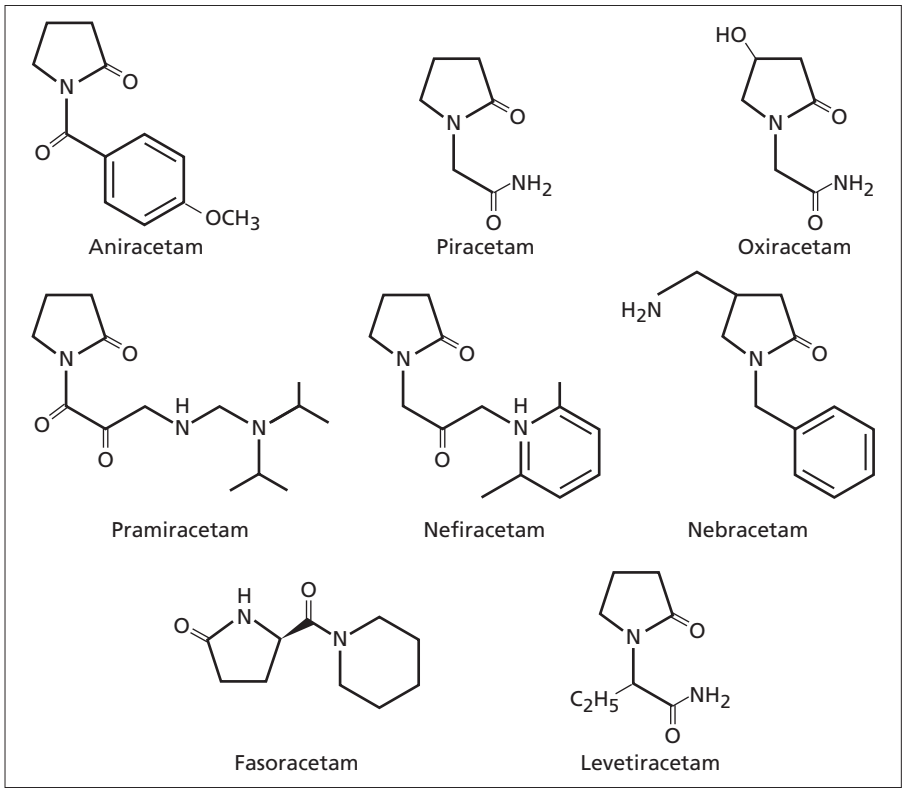

Fig. 48.1 Structure of piracetam and seven other pyrrolidone drugs which are either licensed or in clinical development.

the geographical differences are likely to be due to cultural and regulatory factors, it remains at least possible that there are racial differences in drug response for the class as a whole, although these have been investigated in relation to the antiepileptic effects of levetiracetam without striking differences observed.

In the field of epilepsy, the newer pyrrolidone derivative, levetiracetam, has in the last few years occupied centre stage and, in parallel, interest in piracetam has diminished. It is clear that levetiracetam's antiepileptic effects greatly exceed those of piracetam. However, piracetam does have a marked antimyoclonic effect, which is the main focus of this chapter.

The remarkable antimyoclonic effect of piracetam was first reported in 1978 in a case of post-anoxic myoclonus after cardiac arrest [4], and in the past decade the effectiveness of this drug in cortical myoclonus of various aetiologies has been confirmed. Its use in epilepsy is confined to this indication.

A striking pharmacological feature of pyrrolidone derivatives is their stereospecificity [5]. Minor changes in structure result in remarkable differences in pharmacological activity (Fig. 48.1). Levetiracetam, which is closely related to piracetam, exhibits quite different cerebral binding and broad-spectrum antiepileptic properties (see Chapter 44). Levetiracetam also has an antimyoclonic effect, although it is not clear whether this differs from that of piracetam. Other drugs in this class (e.g. nefiracetam, brivaracetam and seletracetam) also have antimyoclonic and antiepileptic properties, and are in various stages of development.

A notable aspect of the whole class is their relatively good tolerability. This has been an important impetus to further study, and remains one of the primary attractions of this drug class.

Chemistry and mechanism of action

Piracetam, 2-oxo-1-pyrrolidine acetamide, is a white, almost odourless crystalline powder. It is closely related to levetiracetam (which is the ethyl ester of the laevo isomer of piracetam). Since the launch of levetiracetam, there has been major experimental effort designed to elucidate the antiepileptic effect of this drug and, by extension, of the whole drug class. These agents do not, like some antiepileptic drugs, bind to the $GABA_A$–benzodiazepine receptor complex, do not inhibit voltage-gated Na^+ channels and do not inhibit low voltage-gated T-type Ca^{2+} channels. Levetiracetam and its derivatives have been found to bind to the SV2A protein [6], which is one of the three isoforms of the SV2 protein, and the isoform most widely distributed in brain (levetiracetam does not bind to the other two isoforms). The SV2A protein is present in the membrane of synaptic vesicles at the presynaptic terminal. Its role in synaptic transmission is not clear, but it is hypothesized to modulate maturation and/or fusion of vesicles with the plasma membrane of the presynaptic terminal, and to control vesicle exocytosis. There is a strong correlation between affinity of pyrrolidone derivatives for the SV2A binding site and seizure protection in animal models of seizures and epilepsy (Fig. 48.2) [6]. There are no published studies of the molecular mechanisms of action of piracetam, but it is possible that the antimyoclonic actions are related to its weak binding to the SV2 protein.

Piracetam has also been shown to enhance oxidative glycolysis, to have anticholinergic effects, positive effects of the cerebral microcirculation under certain conditions with an increase in cerebral blood flow, effects on membrane physics and also rheo-

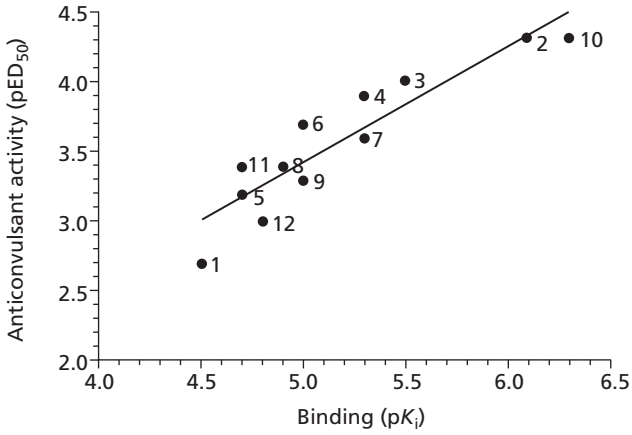

Fig. 48.2 Piracetam has weak binding to the SV2A binding site compared with levetiracetam. Here is shown a comparison between the affinity of (S)homologues of levetiracetam at the [^{3}H]levetiracetam binding site with the anticonvulsant activity of these compounds in the audiogenic mouse test. r^2 = 0.84, $P < 0.0001$, $n = 12$. 1, piracetam; 2, levetiracetam. Reproduced with permission from ref. 48.

logical properties, including reduction of platelet aggregation and changes in erythrocyte properties [1,7–10]. Piracetam may also affect mitrochondrial function. Whether any of these properties contribute to the suppression of myoclonus is quite unclear. Although disturbances of serotonergic and GABAergic function may be implicated in cortical myoclonus, piracetam does not seem to modify GABAergic activity, or affect cerebral serotonin or dopamine levels.

Pharmacokinetics

The pharmacokinetics of piracetam has been relatively extensively characterized in humans, and found to be linear (Fig. 48.3) [11,12].

Absorption

Studies in healthy volunteers have shown rapid and complete absorption after oral administration, with peak plasma concentrations (C_{max}) occurring at between 30 and 50 min. C_{max} values are 15–37 mg/L after a single dose of 800 mg, and 30–54 mg/L after a dose of 1600 mg.

Distribution

The volume of distribution of piracetam is 0.5–0.75 L/kg, and there is no significant binding to plasma proteins. Piracetam crosses the blood–brain barrier with a delayed peak, and the mean half-life in cerebrospinal fluid is 7.7 h after intravenous injection in healthy volunteers. The drug crosses the placental barrier freely. The distribution of the molecule has been investigated in the rat with radioactive labelled drug, with some evidence of preferential concentration in brain.

Metabolism and excretion

Piracetam does not undergo any known metabolism, although Hitzenberger *et al.* [11] postulate that some degree of metabolism must occur. The drug is largely excreted unchanged through the kidneys, with renal excretion accounting for 65–100% of the dose in various studies, after both acute and chronic administration (Fig. 48.4). After oral administration of single doses between 800 and 1200 mg, an elimination half-life of 4–5 h is found, and similar findings have been reported in the elderly.

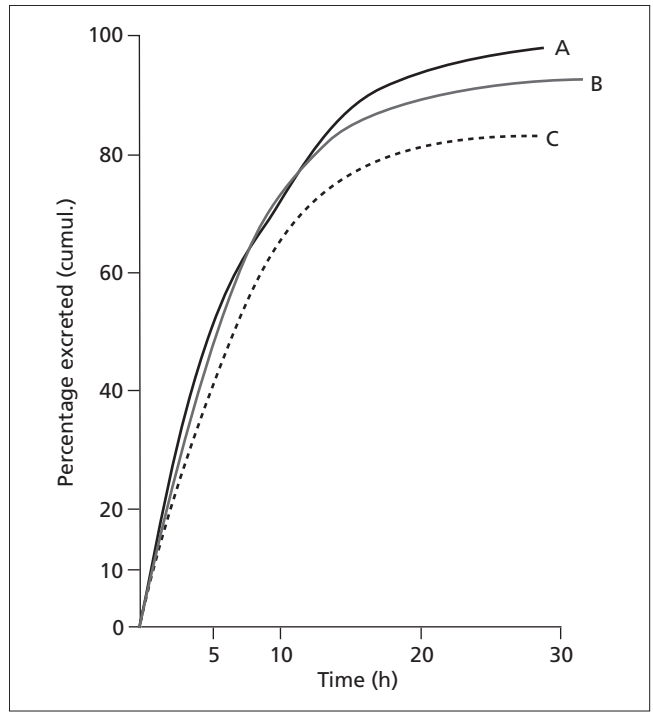

Fig. 48.3 Urinary excretion of radiolabelled piracetam in three subjects following a single oral dose of 2 g. From the manufacturer's literature.

Drug interactions

No drug interactions have been recorded, and none indeed would be expected in view of the lack of metabolism or protein binding and its mode of elimination. Over the years, the studies of potential interaction have included co-medication with antibiotics, antiepileptic drugs, muscle relaxants, corticosteroids, antifibrinolytic drugs, antidepressants, antihypertensive drugs and hormone replacement therapy.

Serum level monitoring

No adequate data on the potential usefulness of serum drug level monitoring are available.

Efficacy

An *n*-of-1 clinical trial can provide compelling evidence of efficacy in myoclonus, as the jerks are often so frequent and so intrusive that the effectiveness of therapy can be immediately apparent. So

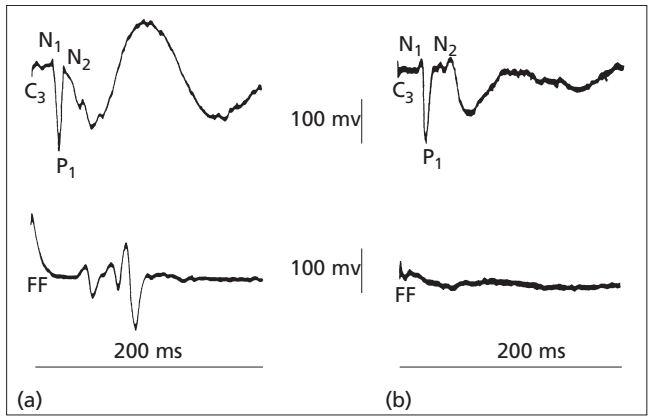

Fig. 48.4 Giant cortical somatosensory evoked potential to electrical stimulation of the forefinger and the reflex EMG discharge recorded from the finger flexor (FF) muscles of the right arm in a patient with stimulus-sensitive cortical action myoclonus. (a) Prior to treatment with piracetam, and (b) following treatment, showing the abolition of the reflex myoclonus after treatment with oral piracetam (8 g/day). From ref. 23 with permission.

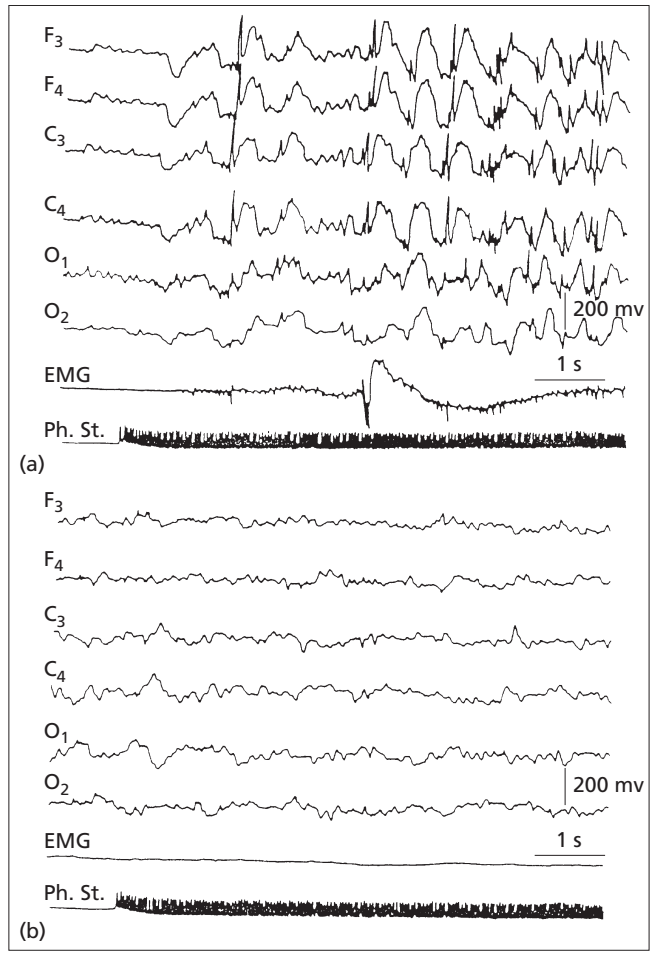

Fig. 48.5 EEG from a patient with stimulus-sensitive cortical action myoclonus (a) before and (b) after piracetam treatment. The pretreatment EEG shows spike-and-wave activity associated with generalized muscle jerks, induced by photic stimulation at 18 flashes/s. The post-treatment EEG shows a complete suppression of the spike–wave bursts and also the reflex myoclonic jerking after oral treatment with piracetam on 9 g/day for 7 days. From ref. 23 with permission.

was the case with piracetam: the first case report demonstrating an unequivocal antimyoclonic effect [4] relates to a patient with severe post-anoxic myoclonus who showed a dramatic acute effect after serendipitous administration of piracetam for another purpose. Subsequent uncontrolled reports in small numbers of patients confirmed this action [13–19]. Following these early anecdotal reports, Obeso *et al*. published a series of studies [20–25] exploring the effects of piracetam in myoclonus more systematically (Figs 48.4 and 48.5). These studies included a series of 40 patients with myoclonus, with differing clinical and electrophysiological features [24], and subsequently a further report of 10 patients extensively studied and treated with up to 18 g/day of piracetam [25]. In 1993, a placebo-controlled double-blind cross-over trial was reported by David Marsden's group, confirming the undoubted effectiveness of the drug in myoclonus [26]. The drug was then licensed for use in myoclonus in the UK and elsewhere.

The 40 patients reported by Obeso *et al*. [24] were heterogeneous. The myoclonus was secondary to anoxia in 12 cases, associated with the Ramsay–Hunt syndrome in five cases, multisystem atrophy in four, torsion dystonia in seven, birth anoxia in three, Creutzfeldt–Jakob disease in two, and occurred in single cases of Alzheimer's disease, herpes encephalitis, Lafora body disease and essential myoclonus. In three cases, the cause was unknown. Piracetam was given as short-term monotherapy to six patients and to the rest in combination therapy (doses used were between 18 and 24 g/day). Of these monotherapy-treated patients, two with cortical myoclonus showed electrophysiological improvement, but none of the four with electrophysiological evidence of subcortical myoclonus improved. Thirty-six patients had piracetam added to existing antimyoclonic therapy, and in 16 there was improvement. A dramatic response was seen in a woman on clonazepam who was bedbound with severe post-anoxic action myoclonus. When piracetam was added she could walk, dress and feed herself; within 2 days of withdrawal of piracetam she was again bedbound. Five out of eight other patients with post-anoxic myoclonus also improved, but less dramatically. All of the 16 patients who showed improvement had cortical myoclonus, and the aetiology underlying the cases varied. Five other patients with cortical myoclonus did not improve, nor did any of the patients with subcortical myoclonus.

The study of Brown *et al*. [26] was a well-conducted double-blind placebo-controlled cross-over trial in 21 patients. All patients had cortical myoclonus and received piracetam up to a maximum dose of 16.8 g per day or placebo for 14-day trial periods, in addition to their routine antimyoclonic therapy. Patients were rated on scales of stimulus sensitivity, motor skills, writing ability, functional disability, and were also scored on global assessments and visual analogue scales. Ten of the 21 patients failed to complete the placebo phase due to a severe exacerbation of their myoclonus, and none during the piracetam phase. Significant improvements were noted in all the scales on piracetam, and there was a median 22% improvement on piracetam on the global rating scale. There were also more seizures of

other types during the placebo phase than during the piracetam phase. These results are impressive and confirm that piracetam can have a marked effect on cortical myoclonus. The study also showed that abrupt withdrawal of piracetam may lead to a marked exacerbation of myoclonus and withdrawal seizures. Longer-term follow-up of some of the patients in these trials has confirmed the effect of piracetam, and in at least one of the cases (treated by the author), the effect was profound and maintained without evidence of tolerance. This 21-year-old patient was under my care with myoclonus and occasional generalized epileptic seizures of unknown aetiology, and was bedbound and dependent prior to piracetam therapy. There was an immediate response to piracetam, and immediate relapse on the three occasions that the drug had been withdrawn. After 12 years of piracetam montherapy (at a daily dose of 21 g) she is still almost entirely free of myoclonus, has completed a university education, produced two healthy babies and lives a normal life. Peuvot [27] reported the effect of piracetam in 13 patients (12 with post-anoxic myoclonus), of whom five were 'cured' and all except one improved. It was also noted that temporary withdrawal of piracetam led to a 'spectacular reappearance of myoclonus'.

A more recent double-blind cross-over study in Finland compared placebo and three dosage regimens of piracetam (each for 2 weeks) in 20 patients with Unverricht–Lundborg disease [28]. A daily dose of 24 g piracetam produced significant and clinically relevant improvement in the primary outcome measures of motor impairment, functional disability, and in global assessments by both investigator and patient. Significant improvement in functional disability was also found with daily doses of 9.6 g and 16.8 g. The dose–effect relation was linear and significant. Piracetam was well tolerated and adverse effects were few, mild and transient. This study confirmed the strong effect of piracetam in this condition and also its tolerability and safety, even at massive doses.

Piracetam is used relatively widely in the Far East and an open Japanese study of 60 patients reported very positive antimyoclonic effects in both monotherapy and polytherapy. Piracetam therapy was also associated with benefits on gait ataxia and convulsions, and with improvements in psychological function such as improved motivation, less sleep disturbance, better attention and less depression. No correlation was found between clinical and electrophysiological improvement [28].

Other reports of effectiveness against myoclonus, often dramatic, have been published in three patients with progressive myoclonic epilepsy [29], in myoclonus due to carbon monoxide poisoning [30], in two sisters with myoclonus due to sialidosis type 1 [31], in six cases of dyssynergia cerebellis myoclonica [32], in post-electrocution myoclonus [33], in three patients with Huntington's disease and myoclonus [34] and in myoclonus of the trunk [35]. A recent Russian publication reports a very positive effects on *epilepsia partialis continua* in six children with Kozhevnikov epilepsy given piracetam by daily intravenous infusions, up to a dose of 35 g/day, for 30 days. On this regime, three children improved by 75% or more and three became free of myoclonus. There was also an improvement in other seizures and in the severity of the hemiparesis. The clinical improvement was said to persist for up to 2 months after the cessation of the infusion [36].

Cortical myoclonus, with or without additional epilepsy, can result in profound disability. The jerks are often exacerbated by action, and the patients may be bedbound and immobile, unable to move without severe myoclonic jerking disrupting all motor responses. In some cases, piracetam can have a truly remarkable effect, suppressing the myoclonus, and reversing completely even severe disability. In such patients, the drug is nearer to a 'magic bullet' than any other of which I have experience.

The comparative effectiveness of piracetam and levetiracetam has not been formally assessed, although this would be an important and interesting study. Anecdotally, I have a patient with non-epileptic myoclonus who responded to piracetam but not levetiracetam, but other cases of idiopathic generalized epilepsy in whom levetiracetam had a greater antimyoclonic effect than piracetam. Indeed, there are no systematic studies of piracetam in the myoclonus of idiopathic generalized epilepsy (e.g. in juvenile myoclonic epilepsy), nor comparative trials of piracetam and levetiracetam, although these would be of interest given the efficacy of levetiracetam in idiopathic epilepsy, which has been clearly demonstrated in a randomized controlled study [37]. The effect of piracetam on other types of seizures has not been studied in a controlled fashion, although anecdotal experience is disappointing.

There does not appear to be tolerance to the antimyoclonic effect, but withdrawal of medication will often return the patient to the pretreatment state within a few days [38]. Whether or not the effects are confined to cortical myoclonus is uncertain, and I have personal cases with myoclonus, controlled by piracetam, which were more likely to be subcortical in origin. Not all patients with cortical myoclonus respond to the drug, and what differentiates these cases from others is unclear. It has been said that the drug works best in combination, for example with clonazepam, although personal and anecdotal experience shows that piracetam monotherapy can be highly efficacious.

Adverse effects

Because of piracetam's extensive use as a cognitive enhancer, there is considerable experience of its clinical tolerability, at least at low dosages. The drug seems well tolerated, and even in placebo-controlled trials, adverse effects were often reported at a greater frequency with placebo than with the active drug [26]. In these studies, the most commonly reported adverse effects include dizziness, insomnia, nausea, gastrointestinal discomfort, hyperkinesis, weight gain and agitation (all reported at a frequency of less than 10%). Rash occurs in less than 1% of patients, and there have been no serious idiosyncratic reactions. In the placebo-controlled double-blind cross-over study of Brown *et al*. [26], the only adverse events were sore throat and headache in one patient, and single seizures in two; these effects may not have been treatment related. In the routine treatment of myoclonus, it is not uncommon to use daily doses of up to 24 g or more, and the adverse effect profile at these doses is much less well studied. Anecdotal clinical evidence suggests that most patients tolerate even these high doses well, and that adverse effects are rarely a serious problem. In controlled trials there have been no significant effects on haematological or biochemical parameters, although

anecdotal cases of haematological disturbances are reported [28].

Place in current therapy

Piracetam is available in 800- and 1200-mg white tablets or as a solution of 200 mg/mL or 333.3 mg/mL. In myoclonus, early clinical series used doses which were high by previous standards, but modest by current standards: Terwinghe *et al*. [4] used 4.8 g/day in the first reported case, and other studies used doses of 6.4 g/day [36], 8–9 g/day [16,21,24] and 10 g/day [13,29,32,35]. More recently, higher doses have been used – up to 16.8 g/day [27] or up to 18 g/day [26]. In my personal clinical practice, doses of up to 32 g/day are not uncommonly used, and occasionally even higher doses. The optimal dosage is therefore unclear, but it would seem sensible to recommend initial doses of between 4.8 and 8.0 g/day, and to progressively increase the dose to up to 24 g/day, guided by clinical response, and then to higher doses if required. The drug can be given in two or three divided doses, its major drawback at higher doses being the number of tablets taken and their bulk. For other indications, lower doses are used.

It is usual to reserve piracetam therapy as a third line for patients resistant to treatment with valproate or benzodiazepines and, more recently, levetiracetam. However, some authorities recommended it as first-line therapy in myoclonus [37,39], and its effectiveness in some patients, combined with its almost complete lack of adverse effects, give the drug a special place in antimyoclonic therapy. The recent licensing and greater convenience of levetiracetam, however, may well usurp the place of piracetam. However, there are no comparative studies and the role for piracetam in relation to levetiracetam has not been defined.

As mentioned earlier, piracetam has been widely used clinically for other indications. Its cognitive-enhancing properties have been the subject of numerous open studies but most were uncontrolled and do not meet modern assessment standards. About 50 controlled studies exist, with some showing modest benefits, but others are negative. A Cochrane meta-analysis in 1998 concluded that evidence of effects on cognition and other measures was inconclusive [40]. There are ongoing studies of piracetam in the syndrome of mild cognitive impairment. A distinctive neuroprotective function, separate from cognitive enhancement, has been demonstrated experimentally. Both properties clearly carry promise for use after stroke to limit functional impairment and for rehabilitation. Initial uncontrolled clinical evidence, as well as experimental evidence, in acute stroke had been encouraging [41–47], but a major controlled trial of 927 patients randomized to placebo or piracetam (12 g intravenous, followed by 12 g daily for 4 weeks and 4.8 g daily for 8 weeks) showed no difference in the primary or secondary endpoints (neurological outcome after 4 weeks or functional outcome after 12 weeks) [47]. It is possible that earlier treatment confers more benefit, and also that those with more severe symptoms following stroke do better than those with mild symptoms, and also those with aphasia [46,47].

There is little experience of piracetam in pregnancy, but as the drug readily crosses the placenta and into breast milk, it should probably be avoided in pregnancy and lactation. As piracetam is almost exclusively excreted by the kidneys, the dose should be lowered in patients with renal impairment. Recommended adjustments are a 50% reduction in dose at creatinine clearances of 40–60 mL/min (serum creatinine of 112–153 μmol/L) and a 75% reduction at creatinine clearances of 20–40 mL/min (serum creatinine of 153–270 μmol/L). The drug is contraindicated in patients with creatinine clearances below 20 mL/min, and in those with severe hepatic impairment. There is little published experience of the drug in children.

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49 Pregabalin

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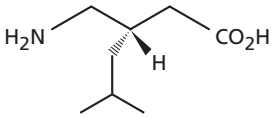

Primary indications	Adjunctive therapy for partial seizures with or without secondary generalization
Usual preparation	Capsules: 25, 50, 75, 100, 150, 200, 300 mg
Usual dosages	Initial: 150 mg/day. Maintenance: 150–600 mg/day
Dosing frequency	2 or 3 times/day
Significant drug interactions	Pregabalin may potentiate the effects of other CNS depressants on cognition and motor coordination
Serum level monitoring	Not routinely used. Dosage is generally adjusted on the basis of clinical response
Reference range	Not established
Common/important adverse effects	Dizziness, somnolence, ataxia, asthenia, weight gain, visual disturbances, difficulty concentrating, tremor, peripheral oedema
Main advantages	Robust efficacy, predictable pharmacokinetics, lack of drug interactions and activity in neuropathic pain, fibromyalgia and generalized anxiety disorder
Main disadvantages	Spectrum of efficacy restricted to partial epilepsies. CNS adverse effects and propensity to cause weight gain
Mechanism of action	Modulates neurotransmitter release by binding to the α_2-δ subunit of voltage-gated calcium channels
Oral bioavailability	>90%
Time to peak levels	1–2 h
Elimination	Renal excretion in unchanged form
Volume of distribution	Approximately 0.5 L/kg
Elimination of half-life	5–7 h
Plasma clearance	0.7–1.0 mL/min/kg
Protein binding	Nil
Active metabolites	None
Comment	A useful antiepileptic drug for the management of refractory partial-onset seizures

Introduction

Pregabalin is one of the latest agents introduced for the management of partial epilepsy in adults. Marketing authorization was granted by the European Medicines Agency (EMEA) in July 2004, and by the US Food and Drug Administration (FDA) in June 2005, for use as add-on therapy for the treatment of partial seizures with or without secondary generalization. Pregabalin is also used, or proposed for, the treatment of neuropathic pain [1], fibromyalgia [2] and generalized anxiety disorder [3].

Chemistry

Pregabalin, also known as *S*-(+)-3-isobutyl-GABA, is a structural analogue of γ-aminobutyric acid (GABA) and corresponds chemically to (*S*)-3-(aminomethyl)-5-methylhexanoic acid. Its molecular formula is $C_8H_{17}NO_2$ and its molecular weight is 159.23.

Pregabalin has a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is a white to off-white crystalline powder, freely soluble in water and in basic and acidic aqueous solutions. The log of the partition coefficient (*n*-octanol/0.05 M phosphate buffer) at pH 7.4 is –1.35.

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Pharmacology

Activity in animal models of epilepsy and other indications

In all animal models of seizures and epilepsy tested, pregabalin has a similar activity profile to gabapentin, but it is consistently three- to sixfold more potent on a mg/kg dose basis than gabapentin [4]. Thus, pregabalin has been shown to be effective against seizures in a wide range of experimental animal models, exhibiting potent activity against seizures induced by maximal electroshock, pentylenetetrazole, bicuculline and picrotoxin [5–7]. Pregabalin is also effective in preventing seizures in kindled rats, and audiogenic seizures in genetically susceptible (DBA/2) mice, although it is ineffective in genetic animal models of absence seizures such as the Genetic Absence Epileptic Rat of Strasbourg.

Pregabalin also exhibits activity in preclinical models predictive of activity against anxiety and neuropathic pain.

Mechanism of action

The pharmacological effects of pregabalin are believed to result from its binding to the α_2-δ subunit of P-, Q- and N-type voltage-gated calcium channels, resulting in allosteric modulation of the channels, decreased depolarization-induced calcium influx at nerve terminals, and reduced excitatory neurotransmitter release [5,6,8–10].

Although pregabalin is structurally related to GABA, it does not appear to act via the GABAergic system, being inactive at $GABA_A$, $GABA_B$ and benzodiazepine receptors, not converted metabolically into GABA or a GABA agonist, and having no effect on GABA uptake or degradation [5,11].

Pharmacokinetics

Key pharmacokinetic features

In clinical pharmacology studies, pregabalin demonstrated predictable linear pharmacokinetics following oral dosing, with low intersubject variability.

Absorption is rapid, with maximal serum concentrations (T_{max}) occurring approximately 1 h after single or multiple oral doses. Although pregabalin's passage across the gastrointestinal mucosa is mediated by an active transport system which is the same as that responsible for the absorption of gabapentin, within the clinically occurring pregabalin dose range the system does not become saturated and therefore oral bioavailability is virtually complete [5,6]. Steady-state conditions are achieved within 24–48 h following repeated administration [5].

Pregabalin does not bind to plasma proteins, is not significantly metabolized and is excreted virtually entirely in unchanged form by the kidney [5]. The elimination half-life is in the order of 5–7 h and the apparent plasma clearance is in the order of 0.7–1.0 mL/min/kg following oral administration.

Pharmacokinetics in special groups

Since pregabalin is excreted virtually unchanged by the kidney, its clearance is decreased in subjects with renal impairment, proportionally to the reduction in creatinine clearance (CL_{Cr}) [12,13]. Based on pharmacokinetic calculations, a 50% reduction in pregabalin daily dose is recommended for patients with CL_{Cr} between 30 and 60 mL/min compared with those with $CL_{Cr} > 60$ mL/min, and daily doses should be further reduced by approximately 50% for each additional 50% decrease in CL_{Cr}.

Randinitis *et al.* [13] have shown that pregabalin is extensively cleared by haemodialysis. Therefore, supplemental doses may be required for patients on chronic haemodialysis after each dialysis session to maintain unaltered serum pregabalin concentrations.

The influence of age on pregabalin pharmacokinetics does not appear to have been formally investigated. However, since renal function declines physiologically in old age, pregabalin clearance is expected to be reduced in elderly patients in proportion with the reduction in CL_{Cr}. Preliminary data support this prediction [12].

There are no data on pregabalin disposition during pregnancy. Since pregnancy is associated with an increase in glomerular filtration rate, the possibility of a increase in pregabalin clearance during gestation can be anticipated [14].

Drug interactions

Pregabalin is devoid of enzyme-inducing or -inhibiting activity on drug-metabolizing enzymes, and it is not itself significantly metabolized. Therefore, drug–drug interactions are considered unlikely with pregabalin.

Formal drug interaction studies have shown that pregabalin does not affect the serum concentrations of concomitantly administered antiepileptic drugs (AEDs), including carbamazepine, phenytoin, lamotrigine and valproic acid [5,6,15,16]. Serum pregabalin concentrations also do not appear to be affected by concomitant AEDs [15], even though in one study a moderate decrease in pregabalin concentrations (20–30%) was reported in patients co-medicated with enzyme-inducing AEDs [12].

Post hoc population analysis of pharmacokinetic studies has revealed no significant interactions between pregabalin and oral contraceptives, insulin, diuretics or oral hypoglycaemic agents [5,6,15,16]. Additive effects of pregabalin on the impairment of cognitive and gross motor function caused by oxycodone, and potentiation of the effects of ethanol and lorazepam, have been observed (Pfizer, data on file). However, co-administration of multiple oral doses of pregabalin with oxycodone, lorazepam or ethanol did not result in clinically important effects on respiration.

Serum level monitoring

The relationship between serum pregabalin concentrations and clinical effects has not been adequately investigated, and serum pregabalin levels are not routinely monitored during pregabalin therapy [17].

Efficacy in epilepsy

Pregabalin efficacy has been evaluated as add-on therapy in adults with refractory partial epilepsy in short-term randomized controlled trials and in long-term open-label studies. A monotherapy clinical development programme in adult patients with partial epilepsy is currently under way.

Short-term randomized controlled trials

Study designs

The efficacy and safety of pregabalin as add-on therapy in partial seizures with or without secondary generalization has been studied in four randomized, double-blind, placebo-controlled short-term multicentre trials involving 1396 patients with uncontrolled seizures [6,18–24] (Table 49.1).

Three of these studies [18,19,22] (n = 1052) were designed to investigate dose–response relationships by using fixed-dose regimens (Table 49.1). The data from these three trials were then used to define a minimum effective dose and an approved dosing regimen as required by regulatory authorities. In the first of these studies [22], 453 patients (≥12 years old) in Canada and the USA were randomized to receive placebo or 50, 150, 300 or 600 mg/day pregabalin administered as two divided doses, with no titration period. In the second international study [18], 287 patients (≥18 years old) received placebo or 150 or 600 mg/day pregabalin administered in a three times daily regimen, with up to 1 week of titration. The third fixed-dose study [19] involved 312 patients (≥18 years old) randomized to receive placebo, pregabalin 600 mg/day twice daily or pregabalin 600 mg/day three times daily, each with up to 1 week of titration.

The fourth study was a 12-week placebo-controlled trial [21], which differed from the earlier trials in that it was designed to more closely represent pregabalin's potential use in real-world management settings by comparing a flexible dose regimen with a high-dose fixed-dose regimen, both given in two divided daily doses. In total, 341 patients aged 18 years and above were randomized to receive adjunctive twice-daily dosing with either placebo, a fixed pregabalin dose of 600 mg/day, or a flexible pregabalin dose of 150–600 mg/day (Table 49.1 and Fig. 49.1). Patients randomized to the pregabalin fixed-dose group received 600 mg/day for the entire double-blind treatment period. Patients randomized to the pregabalin flexible-dose group started on 150 mg/day pregabalin for the first 2 weeks, and then increased

Table 49.1 Characteristics of short-term randomized placebo-controlled adjunctive therapy trials of pregabalin in patients with partial seizures.

Study	Pregabalin dose	Trial duration (weeks)			Number of patients (intent to treat)			Gender (%)		Baseline seizure frequency (median/month)	Location
		Baseline	Double-blind	Titration	Total	Pregabalin	Placebo	Male	Female		
French *et al.* [22]	50 mg/day[a] 150 mg/day[a] 300 mg/day[a] 600 mg/day[a]	8	12	–	455	88 88 90 89	100	47.9	52.1	10	Canada, USA
Arroyo *et al.* [18]	150 mg/day[b] 600 mg/day[b]	8	12	1	288	99 92	97	50.3	49.7	11	Australia, Europe, South Africa
Beydoun *et al.* [19]	600 mg/day[a] 600 mg/day[b]	8	12	1	313	104 111	98	49.8	50.2	10	Canada, USA
Elger *et al.* [21]	Fixed 600 mg/day[a] Flexible 75–600 mg/day[a]	6	12	– Flexible, 12 weeks	341	131 137	73	49.9	50.1	9	Canada, Europe

[a] Given in two divided doses.
[b] Given in three divided doses.

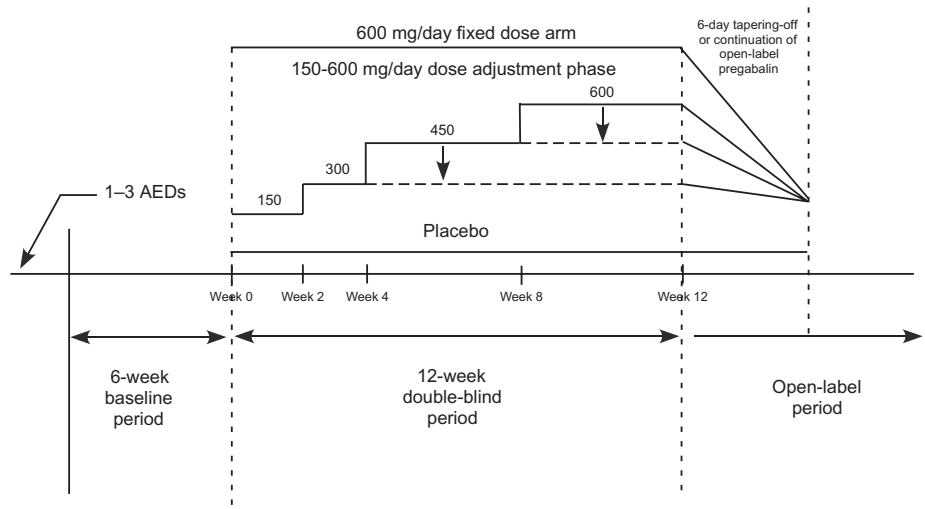

Fig. 49.1 Design of the trial comparing pregabalin at flexible doses (150–600 mg/day) with a fixed dose (600 mg/day) as adjunctive therapy in refractory partial epilepsy. From ref. 21 with permission.

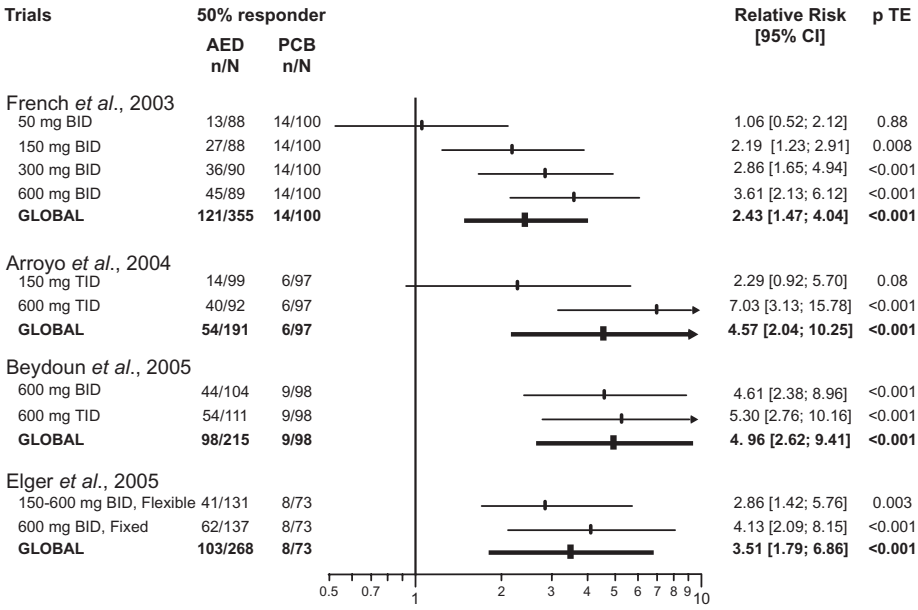

Fig. 49.2 Proportions of patients achieving at least 50% seizure reduction (50% responder rates) in short-term randomized adjunctive therapy trials of pregabalin in refractory partial epilepsy. Relative risks and 95% confidence intervals (CIs) for responder rates are also shown. Indicated doses are total daily doses (BID and TID indicate that the specified dose was divided into two or three daily administrations, respectively). AED, pregabalin; PCB, placebo, pTE, *P*-value for the treatment effect. Adapted from ref. 40.

to 300 mg/day for the next 2 weeks. Patients who were seizure free then remained on 300 mg/day for the remainder of the study as directed by the investigator, whilst those still having seizures increased their dose to 450 mg/day for the next 4 weeks. Similarly, at week 8, seizure-free patients remained on 450 mg/day, whilst those still having seizures increased their dose to 600 mg/day. At any point after the first 4 weeks, patients who experienced intolerable adverse events could reduce their daily dose to the previous level for the remainder of the treatment period. Thus, after the first few weeks, these patients received a pregabalin dose that was optimized both for efficacy in reducing seizure frequency and for tolerability.

All the patients enrolled in each of these four studies were highly refractory to treatment. Patients entering the three fixed-dose studies were required to have a history of failing two or more AEDs at maximally tolerated doses and to experience six or more partial seizures and no 4-week seizure-free period during the 8-week baseline phase [18,19,22]. For the fourth flexible-dose study, patients were required to have four or more partial seizures and no 4-week seizure-free period during the 6-week baseline [21].

Efficacy in the fixed-dose trials

Enrolled patients in fixed-dose trials had a mean duration of epilepsy of 25 years and were highly refractory to treatment, with a mean baseline seizure rate of 24.4 seizures per month (median 11.2 per month) and with 73% of them taking at least two AEDs [20,24].

In each of the three fixed-dose studies, add-on therapy with pregabalin (dosed twice and/or three times daily) was found to be effective against refractory partial seizures [18,19,22]. In particular, doses of 150, 300 and 600 mg/day were significantly superior to placebo in reducing seizure frequency, whilst the 50 mg/day dose was not effective [18,20,22,24]. Thus, the minimum effective dose was established as 150 mg/day, and this was shown to be statistically different from placebo given as either two or three divided doses. A statistically significant dose–response relationship for seizure reduction was also demonstrated in both of the dose-finding studies ($P < 0.0001$ for each study). Twice-daily and three times daily dosing regimens displayed similar efficacy in terms of seizure reduction.

Responder rates (proportions of patients with ≥50% reduction from baseline seizure frequency) across the effective pregabalin doses (150–600 mg/day) ranged from 14% to 51% (Fig. 49.2), and also demonstrated a clear and significant dose–response relationship. The number of background AEDs or the baseline seizure frequency had no influence on the responder rate.

Pooled data for the proportion of seizure-free patients on each study day across the three fixed-dose studies indicated that pregabalin has a rapid onset of action. For the effective pregabalin doses (150–600 mg/day), a significant reduction in seizure activity compared with placebo was observable by day 2, and this persisted throughout the 12-week evaluation period [25]. Between 3% and 17% of patients receiving effective pregabalin doses in each of the three fixed-dose trials were free from seizures during their last 28 days of treatment (compared with between 0% and 1% of those receiving placebo), with seizure-free rates tending to increase with increasing dose [20]. Furthermore, in two separate studies, seizure freedom rates in patients receiving pregabalin 600 mg/day in three divided doses were statistically significant compared with those in placebo-treated patients [18; Pfizer, data on file]. When the seizure-free period was extended to include the entire double-blind treatment period for the modified intent-to-treat (ITT) population, pregabalin doses of 300 or 600 mg/day were each significantly more effective than placebo, with seizure-free rates of 8% for the 300 mg/day dose (one study) and between 7% and 19% for the 600 mg/day dose (three studies). Furthermore, in the two dose-finding studies, seizure-free rates for the double-blind treatment period tended to increase with dose. Seizure-free rates for the entire double-blind period for patients

who completed the study ranged between 1% and 5% for the 600 mg/day dose.

Overall, these three short-term trials provided proof of efficacy for adjunctive pregabalin using several different endpoints (seizure reduction, responder rate and seizure-free rate), and also provided some valuable dosing-related data. The minimum effective dose in these studies was 150 mg/day, which was effective when given as either two or three divided doses. An effect of pregabalin was detectable as early as day 2, so patients would be expected to obtain benefit soon after starting treatment. These studies have also demonstrated a clear and significant dose–response relationship for pregabalin in this patient population, meaning that escalating the dose should provide additional efficacy for patients who can tolerate pregabalin and whose seizures are not effectively controlled by the starting dose.

Efficacy in the flexible-dose trial

In the study that compared a fixed dose (600 mg/day) with a flexible-dose regimen (150–600 mg/day) in patients with partial seizures, both dosing regimens were found to be significantly more effective than placebo in reducing seizure frequency. Seizure frequency reductions from baseline were 35.4% in the flexible-dose group ($P = 0.0091$) and 49.3% in the fixed-dose group ($P = 0.0001$), compared with 10.6% in the placebo group [21]. Responder rates were also significantly greater in both the fixed-dose (45.3%, $P < 0.001$) and flexible-dose (31.3%, $P < 0.001$) groups than in the placebo group (11.0%) [21]. During the last 28 days of treatment, 12.2% of patients in the pregabalin flexible-dose group, 12.4% in the fixed-dose group and 8.2% in the placebo group were completely free of seizures.

Responder rates in this study compare well with those observed in the three fixed-dose studies (Fig. 49.2), and provide further support for the efficacy of pregabalin as add-on therapy for partial seizures.

Long-term studies

The long-term efficacy of adjunctive therapy with pregabalin at doses ranging from 75 to 600 mg/day has been evaluated in four long-term, open-label, extension studies. An interim analysis obtained whilst the four studies were still ongoing has been published [6,24]. Since then, all four trials have been completed, and data from the final analysis of the full data set are presented below (Pfizer, data on file).

In total, these trials included 1480 patients with an overall exposure to pregabalin of 3150 patient-years. Prior to participating, most patients ($n = 968$) had previously completed one of the double-blind, randomized, fixed-dose pregabalin trials or an inpatient monotherapy study. Three of the open-label studies also allowed *de novo* entry of patients ($n = 512$). Approximately 2–3.5 years after the open-label studies began, the FDA requested that continuing participation in the studies at US sites be restricted to patients refractory to other AEDs who were responding to pregabalin (i.e. having at least a 30% reduction in seizure frequency compared with baseline). This requalification somewhat complicates the interpretation of the efficacy data, because it creates a bias in favour of pregabalin when assessing patients continuing on long-term treatment. For this reason, seizure data collected after requalification have not been included in the analyses of efficacy, with the exception of seizure freedom data. Seizure freedom analyses have been performed both on data collected prior to initial requalification and on all open-label data for the ITT patients.

By the completion dates of the studies, 77% of patients had received at least 24 weeks of pregabalin treatment whilst 59% had received at least 1 year of treatment, and 35% had received at least 2 years. Approximately 20% of the patients had been studied for at least 5 years. A total of 71% of pregabalin exposures in terms of total patient-years was at doses of 450 mg/day or greater and 48% of pregabalin exposures occurred at the 600 mg/day dose. Approximately half of the patients were taking two other AEDs at the start of the open-label period. In total, 188 patients had to withdraw because of failure to meet the requalification criteria (13% of 1480 enrolled, 44% of the 431 assessed for requalification).

When seizure freedom data for the whole ITT population were analysed, there was an increase in the mean number of seizure-free days per 28 days, from 18.3 days at baseline to 21.5 days during open-label treatment, which represents a mean improvement of 41.6% in seizure-free days for individual patients. In patients who took treatment for at least 6 months or 1 year, 9.2% (103/1119) were seizure free for the last 6 months, and 8.1% (71/877) for the last 12 months, respectively (Fig. 49.3). As discussed previously, the requirement for a response to pregabalin in the US requalification process means that data for the whole population may be biased in favour of pregabalin. Thus, seizure freedom parameters were also analysed by excluding all data collected after requalification, in an attempt to remove any such bias. In this analysis, there was a similar increase in the mean number of seizure-free days/28 days, from 18.3 days at baseline to 21.6 days during open-label treatment. This represents a mean improvement of 39.2% for individual patients. Seizure-free rates were slightly lower in this analysis, with 7.7% (69/892) of patients remaining seizure free over their last 6 months of pregabalin treatment and 3.7% (26/710) being seizure free over the last year. The number of patients remaining seizure free for at least 6

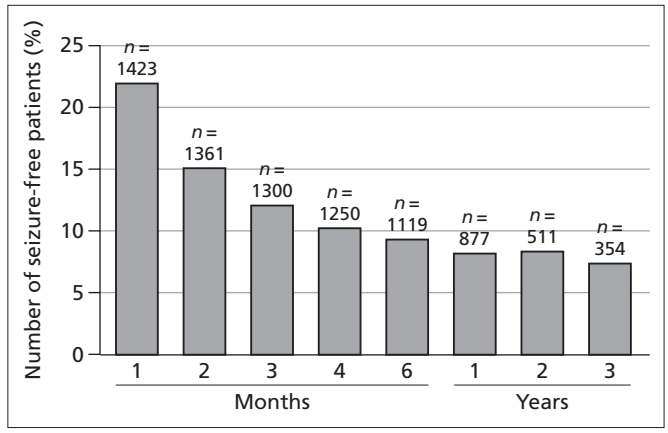

Fig. 49.3 Seizure freedom rates in patients treated with long-term pregabalin in the pooled data set from four open-label trials (entire intent-to-treat population). Numbers in bars indicate duration of seizure freedom in the period preceding the last study visit.

months, or at least 1 year, are particularly encouraging for long-term management, since in many countries these are the seizure-free periods needed to receive a driving licence.

During the initial 12-week period of open-label treatment, the 50% responder rate for the evaluable population who had previously completed one of the three short-term fixed-dose studies was 37%. At subsequent intervals (up to 4 years of open-label treatment), responder rates among patients still treated with pregabalin ranged between 41% and 66%. In the subset of patients who had remained in the study for 2 years, the responder rate during the initial 12-week period of open label was 52%, with responder rates at subsequent intervals remaining at between 50% and 58%. A similar pattern was observed for cohorts of patients who had remained in the study for 6 months or for 1 year. Though these observations might suggest that little or no tolerance to pregabalin develops with long-term exposure, they must be interpreted with caution due to the important number of patients who discontinued treatment, with responders more likely to remain in the study than non-responders. In addition, changes in co-medication often occurred during these long-term studies, and might also play a role in the apparent stability of seizure control over time.

Efficacy in other indications

There is evidence from placebo-controlled randomized trials that pregabalin is effective in the treatment of neuropathic pain syndromes [1,26–28], particularly postherpetic neuralgia and painful diabetic neuropathy [26,27]. Pregabalin is also effective in the treatment of fibromyalgia and other chronic musculoskeletal pain [2,29–31] and in the treatment of generalized anxiety disorder or social anxiety disorder [3,32].

Adverse effects

Tolerability data from short-term fixed-dose placebo-controlled studies

The most frequently reported adverse events in pregabalin-treated patients in double-blind trials were central nervous system (CNS) related (Table 49.2). These events were usually mild or moderate in intensity, generally self-limiting and clearly increased in frequency with increasing dose. Dizziness and somnolence were reported in 28.9% and 20.8% of pregabalin patients, and caused discontinuation in 5.3% and 3.3% of all patients, respectively. Complaints of imbalance, reported in 9.6% of all patients, were significantly increased in pregabalin-treated patients in comparison with placebo-treated patients, with a relative risk of 3.14 [95% confidence interval (CI) 1.37–7.19] for all doses and 5.26 (2.24–12.38) for the highest doses [33]. In general, these adverse events occurred during the first 2 weeks of treatment and then resolved with continued treatment [25]. Overall, withdrawal rates due to adverse events were 15.3% for pregabalin-treated patients and 6.1% for placebo-treated patients [20,24], and few patients (≤5% in any treatment group) discontinued due to lack of efficacy. The relative risk of withdrawal (pregabalin versus placebo) due to adverse events was 2.47 (1.80–4.17) [23]. Most patients (86.6%) elected to enter the open-label extension studies.

There was a strong relation between the occurrence of adverse events and the pregabalin dosage (Table 49.2). In addition, subgroup analyses assessing treatment withdrawal for adverse events with differing doses of pregabalin suggested a higher withdrawal rate with higher doses [23]. Thus, in patients receiving doses of 50 mg or 150 mg/day, the withdrawal rate for adverse events did not significantly differ between placebo and treatment arms. By contrast, the relative risk of withdrawal (pregabalin versus placebo) due to adverse events was 2.89 (1.07–7.78) with a dose of 300 mg/day and 3.74 (2.44–5.74) with a dose of 600 mg/day [23].

Weight gain was reported as a common adverse event, and was spontaneously reported in 10.4% of pregabalin-treated patients compared with 1.4% of placebo-treated patients. In these studies, body weight was also measured at baseline and at last observation, and considered clinically significant if ≥7% over baseline. Eighteen per cent of patients treated with pregabalin and 2.1% of patients treated with placebo presented such significant weight gain, with the majority of patients not gaining more than 10%. Overall, pregabalin-treated patients in these studies gained a mean of 2.1 kg, whereas there was no change in the weight of placebo-treated patients. In those patients who did gain weight with pregabalin, the weight gain appeared to be dose related.

Table 49.2 Most common adverse events (frequency, %) in short-term fixed-dose clinical trials of pregabalin as adjunctive therapy.

	Pregabalin daily dose					Placebo [18,19,21,22] (*n* = 294)
	50 mg [22] (*n* = 88)	150 mg [18,22] (*n* = 187)	300 mg [22] (*n* = 90)	600 mg [18,19,21,22] (*n* = 533)	Flexible, 150–600 mg [21] (*n* = 131)	
Dizziness	9.1	17.6	31.1	33.8	24.4	10.5
Somnolence	10.2	11.2	17.8	25.5	19.1	10.9
Ataxia	3.4	5.9	10	19.9	9.2	4.1
Fatigue	5.7	10.7	12.2	18	16.8	8.2
Headache	6.7	7.5	5.6	10.1	13.7	11.6
Weight gain[a]	1.1	4.8	6.7	17.1	19.1	1.4
Withdrawal for adverse events	6.9	5.9	14.4	24.2	12.2	6.3

Pooled data from four studies [18,19,21,22]. Some patients reported more than one adverse event.
[a]Weight gain spontaneously reported as an adverse event by patient.

There was, however, no apparent association between weight change and changes in blood lipids or loss of glycaemic control. Very few patients (0.4% and 0.0% of pregabalin- and placebo-treated patients, respectively) discontinued during the double-blind phase as a result of weight gain.

There were no deaths during the double-blind periods of these short-term controlled trials.

Tolerability data from the flexible-dose placebo-controlled trial

Fixed-dose trials identified an adjunctive dose of 150 mg/day as an effective starting dose capable of reducing seizure frequency in a significant proportion of patients. In practice, however, it is likely that many patients will require higher maintenance doses to achieve optimal seizure control, and these doses have been associated with a higher incidence of adverse effects in short-term trials. Clinical experience has shown that adverse effects associated with some other commonly used AEDs may be avoided with gradual slow dose escalation [34]. Thus, one of the later pregabalin trials [21] explored whether a flexible dose-escalation regimen (from 150 mg/day up to a maximum of 600 mg/day) would enhance the tolerability of pregabalin while maintaining efficacy compared with a 600 mg/day dose given without titration (for a description of trial design, see Fig. 49.1 and the subsection 'Study designs' in the 'Efficacy' section).

As in short-term fixed-dose trials, the most common adverse events experienced by the fixed-dose group in this trial were dizziness, ataxia and weight gain (43.1%, 21.2% and 20.4%, respectively), while those reported by the flexible-dose group were dizziness, somnolence and weight gain (24.4%, 19.1% and 19.1%, respectively) [21]. As expected, there was a tolerability advantage with flexible dose adjustment, with lower overall rates of discontinuation due to adverse events in the flexible-dose group than in the fixed-dose group (12.3% versus 32.8%). Kaplan–Meier plots estimating the time to exit due to adverse events revealed that patients in the fixed-dose group withdrew from the study sooner and at a greater rate than those in the flexible-dose group ($P = 0.0001$). Only 3% of patients in the flexible dose group and none in the placebo group withdrew due to adverse events in the first week of treatment, compared with 24% of patients in the pregabalin fixed-dose group.

The results from this study suggest that a flexible stepwise dose escalation from a starting dose of 150 mg/day may help to improve tolerability in patients who would ultimately benefit from a higher dose, and can also encourage patients to continue taking medication. It is worth noting, however, that the discontinuation data from this study indicate that most of the patients in the fixed-dose group (over 60%) could actually tolerate the maximum 600 mg/day dose from initiation, and so this could also be a realistic option for patients who may need immediate high doses to attain rapid seizure control.

Long-term tolerability and safety data in patients with epilepsy

In total, 1480 patients with an overall exposure to pregabalin of 3150 patient-years were assessed in four long-term open-label studies (for more information on duration of exposure and dosing in long term studies, see the 'Efficacy' section). Overall, the experience of adverse events and tolerability in these long-term studies was consistent with that observed in short-term placebo-controlled trials. In total, 193 patients (13%) withdrew due to adverse events, and these were considered to be treatment related in 160 patients (11%).

Again, the most frequently reported adverse events were CNS related, with symptoms experienced by ≥5% of all pregabalin-treated patients, including dizziness, somnolence, ataxia, thinking abnormal (a coded term used to indicate difficulties with concentration), tremor, amnesia, depression, insomnia, nervousness, anxiety and confusion. Other frequent adverse events related to the body as a whole included accidental injury, infection, headache, asthenia and pain, although these were not judged to be treatment related. Amblyopia and diplopia were the most frequently reported vision-related adverse events. Painful gynaecomastia and lower extremity pain in association with pregabalin therapy have been reported [35]. A case series of five patients from a single centre suggested that erectile dysfunction and impotence may be an adverse effect of pregabalin [36]. Focal myoclonus has also been reported as a possible adverse effect [37].

Overall, in the open-label extension studies the four most commonly reported adverse events were dizziness, accidental injury, somnolence and weight gain, although very few patients (0.3–2%) reported these events as a reason for withdrawal. Most adverse events were mild or moderate in intensity and usually resolved with continued treatment.

Weight gain was reported as an adverse event overall by 24% of patients. All patients in the four studies were also objectively assessed for body weight changes at their last study visit and at follow-up. The mean weight gain between baseline and study termination was approximately 5 kg, with 44% of patients experiencing a 7% or greater weight increase. Similarly, in a 6-month study which had as primary outcome the assessment of weight gain in patients treated with less than 300–450 mg/day pregabalin, the median body weight gain was 4.0 kg, and 41% of patients who completed the study had a body weight increase of more than 5 kg [38]. Although short-term trials suggested a relation between weight gain and pregabalin dosage (see Table 49.2), long-term studies did not show any correlation of weight gain with absolute dosage (mg/day), relative dosage (mg/kg/day) or categorized dosage (more or less than 300 mg/day) of pregabalin [38]. Conversely, weight gain significantly correlated with the number of AEDs [38]. Finally, this side-effect could not be prevented by extended patient counselling within a standard clinical setting [38].

Serious adverse events were experienced by 246 (17%) open-label patients, although in only 15 patients (1.0%) were these considered by the investigator to be related to pregabalin treatment. Twenty-three patients died during or after the open-label studies; five of these deaths were related to seizures. None of the deaths was considered by the investigator to be causally related to pregabalin treatment.

Tolerability and safety data in other indications

The adverse effects of pregabalin in studies conducted in other indications are similar to those recorded in patients with epilepsy, with the exception of peripheral oedema, which appears to occur more commonly in patients with neuropathic pain than in patients

with epilepsy. In a review of seven randomized controlled trials in painful diabetic neuropathy, the most common treatment-emergent adverse events were dizziness, somnolence and peripheral oedema [26].

In the USA, pregabalin has been designated as a Schedule V controlled substance because of its potential for abuse and dependence, although clinical evidence for such a potential is scarce and this is not a significant consideration when prescribing pregabalin for epilepsy.

Teratogenicity

No adequate information is available on the effects of pregabalin treatment during pregnancy in women with epilepsy. Pregabalin is not teratogenic in mice or rabbits, but teratogenicity was observed in rats at very high doses of 1250–2500 mg/kg, which are much higher than the upper end of the human recommended dose range (Pfizer, data on file).

Place in current therapy

The indications of pregabalin in epilepsy are currently limited to the add-on treatment of adults with drug-resistant partial seizures, with or without secondary generalization. Clinical trials evaluating pregabalin as monotherapy in adults with partial epilepsy, as well as adjunctive therapy trials in children with partial epilepsy, are under way. There is no experience of pregabalin in idiopathic generalized epilepsies, but the potential for seizure aggravation observed with gabapentin is most likely to apply to pregabalin. Thus, pregabalin should not be used in these conditions.

The responder rates observed for pregabalin in short-term randomized controlled trials compare favourably with those seen for other AEDs tested as add-on therapy in refractory populations [39,40]. In a systematic review of all randomized controlled trials performed in adult patients with drug-resistant partial epilepsy, pregabalin was ranked second in efficacy among the 10 most recently developed AEDs [40]. After excluding ineffective dosages from the analysis, pregabalin was associated with the highest relative risk for responder rates, being followed in decreasing order of response by levetiracetam, topiramate, oxcarbazepine, tiagabine, zonisamide, vigabatrin, gabapentin and lamotrigine [40]. However, the confidence intervals of relative risk for all AEDs overlapped, indicating lack of significant differences between the majority of drugs. This is more likely to reflect lack of power of the available data rather than true equivalence between AEDs.

According to its efficacy profile, pregabalin is an appropriate option in the majority of patients with drug-resistant partial epilepsy, including possible use as a first-line add-on therapy. Prior failure to respond to gabapentin does not seem to decrease the chance of responding to pregabalin. There is also no indication of a synergistic action between pregabalin and any other AED that would favour its prescription over that of another drug, as a function of the baseline antiepileptic treatment.

Conversely, the patient's co-morbidities and prior drug-related adverse events may influence the decision on whether pregabalin should be prescribed. In particular, pregabalin is probably not a preferred choice in overweight patients, patients with a past history of AED-triggered weight gain or intolerance to gabapentin, and those with renal dysfunction. In contrast, pregabalin may be considered more appropriate for patients suffering from co-morbid generalized anxiety, insomnia or neuropathic pain. It must be stressed, however, that there is no firm demonstration of beneficial effects of pregabalin in treating such co-morbidities in the specific population of patients with epilepsy.

An effective starting dose for pregabalin is 150 mg/day, which can be given as two divided doses. In patients prone to develop AED-related CNS side-effects, a starting dose of 50 mg/day or 75 mg/day might also be considered, with a 2- to 4-week titration up to 150 mg/day. If needed for additional efficacy, higher doses of 300 mg/day, 450 mg/day, and 600 mg/day may be used, increasing dosage by maximal steps of 150 mg/day over a minimum period of 2 weeks.

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50 Retigabine

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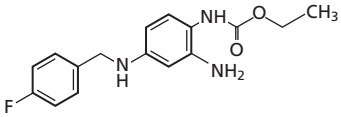

Primary indications	Adjunctive therapy of refractory partial-onset seizures
Usual preparation	Tablets: 50, 100, 200, 300 and 400 mg
Usual dosages	600–1200 mg/day. Treatment may be started with 300 mg/day and increased at weekly intervals by 150 mg/day up to the desired target dose
Dosing frequency	3 times/day
Significant drug interactions	Retigabine decreases serum lamotrigine levels by about 20%. One study suggested that carbamazepine and phenytoin may reduce serum retigabine levels by about 30%, but these interactions were not confirmed in a more comprehensive analysis based on population pharmacokinetics
Serum level monitoring	There is insufficient information on the value of monitoring serum retigabine levels
Reference range	Not clearly defined
Common/important adverse effects	Dizziness, somnolence, fatigue, confusion, dysarthria, ataxia, tremor, blurred vision, nausea, urinary hesitancy/retention
Main advantages	Clearly defined dose-related efficacy in controlled studies, low interaction potential and unique mode of action
Main disadvantages	Need for gradual titration and for three times daily dosing, central nervous system adverse effects and limited clinical experience
Mechanism of action	Activation of voltage-gated neuronal potassium [KCNQ (Kv7)] channels, resulting in enhanced M-current, and thereby stabilization of resting membrane potentials
Oral bioavailability	About 60%
Time to peak levels	0.6–1.5 h
Elimination	Partly by excretion in unchanged form (20–30% of administered dose) and partly by metabolism (50–65% of the dose), including *N*-acetylation and glucuronide conjugation
Volume of distribution	2–3 L/kg (at steady state, as determined with intravenous dosing)
Elimination of half-life	8–10 h
Plasma clearance (CL/*F*)	0.5–0.7 L/h/kg
Protein binding	About 80%
Active metabolites	*N*-acetyl-retigabine (weakly active)
Comment	A potentially valuable drug for the adjunctive treatment of refractory partial-onset seizures. Studies are required to assess potential efficacy in other seizure types

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Introduction

Retigabine is a novel antiepileptic drug (AED) which exhibits unique pharmacological features in that its primary mode of action involves direct activation of the voltage-gated potassium [KCNQ (Kv7)] channels that conduct the M-current, a critical regulator of neuronal excitability. Double-blind, placebo-controlled studies have demonstrated its efficacy as adjunctive therapy in adults with refractory partial-onset seizures. Retigabine is currently in phase III clinical development.

Chemistry

Retigabine corresponds chemically to *N*-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester and it is structurally related to the centrally acting analgesic flupirtine. It is a white to slightly coloured substance with a molecular weight of 303.3 and a pK_a of 3.7 (calculated as free base), poorly soluble in water and soluble in organic solvents.

Pharmacology

Activity in experimental models of seizures and epilepsy

Retigabine exhibits antiseizure effects in an array of *in vivo* seizure/epilepsy models. Rats and mice given retigabine were protected from acute seizures induced by maximal electroshock (MES), low-intensity corneal stimulation (6 Hz; 22, 32 and 44 mA), subcutaneous pentylenetetrazole or picrotoxin, and intracerebroventricular *N*-methyl-D-aspartate (NMDA) [1]. Audiogenic seizures in mice (Frings and DBA/2) and rats (GEPR-3 and -9) were blocked by retigabine [1–3]. In fully kindled rats, retigabine given intraperitoneally (i.p.) raised the afterdischarge threshold (0.01 mg/kg) and reduced behavioural seizure severity (2.5 mg/kg), seizure duration (5 mg/kg) and afterdischarge duration (5 mg/kg) [4]. Effective anticonvulsant doses were widely separated from neurotoxic doses (protective index, 13–14 in the MES threshold test) [1]. The antiseizure effects of retigabine were dose-dependently attenuated by the neuronal KCNQ antagonist XE-991 in the MES model, supporting *in vitro* electrophysiological evidence that activation of neuronal KCNQ M-current is critical to the anticonvulsant activity of retigabine.

Retigabine is active in several models in which seizures do not respond to other AEDs. Specifically, retigabine (20–30 mg/kg i.p.) suppresses seizures in the 6-Hz psychomotor mouse stimulated at either 32 mA or 44 mA [1], although these seizures are resistant to non-toxic doses of lamotrigine, topiramate and carbamazepine (32 and 44 mA), as well as phenytoin, tiagabine and felbamate (44 mA) [5]. In the amygdala-kindling model, the presence of sodium channel blockers carbamazepine [6] or lamotrigine [7] during kindling stimulations rendered post-kindling seizures resistant to carbamazepine, lamotrigine and other AEDs such as phenytoin and topiramate [8]. However, retigabine (20 mg/kg i.p.) was effective against pharmacoresistant post-kindling seizures when lamotrigine was administered during amygdala kindling in rats [9]. The activity of retigabine in models resistant to other AEDs is consistent with retigabine acting at a novel and distinct molecular target.

The amygdala-kindling model has been used to distinguish anticonvulsant activity of AEDs from potential antiepileptogenic effects. Retigabine was not only effective against post-kindling seizures [4], but in several studies it was also found to interfere with kindling-induced increases in seizure susceptibility. When administered before amygdala-kindling stimulations, retigabine (5 mg/kg/day i.p.) retarded kindling acquisition in adult rats [10]. In developing animals, retigabine (2.5 or 5 mg/kg) treatment during the kindling procedure inhibited kindling acquisition in an age-dependent manner [11]. Effects on seizure susceptibility were most prominent at an age corresponding to post-neonatal development in humans, and were also observed at an age corresponding to early childhood but not in more mature ('adolescent') animals.

Activity in experimental models relevant for non-epilepsy indications

Loss-of-function mutations in *KCNQ2/3* genes are associated not only with seizure disorders (benign neonatal familial convulsions) but also with peripheral nerve hyperexcitability (neuromyotonia, neuromyokymia) [12,13]. These channelopathies and the distribution of KCNQ/M-current channels in areas prominently involved in pain signalling (dorsal horn, dorsal root ganglia, afferent peripheral nerves), mood regulation (amygdala) and movement (striatum) underscore the spectrum of disorders beyond epilepsy that may be amenable to treatment with neuronal KCNQ channel openers such as retigabine [14–16].

Although retigabine, an analogue of the analgesic flupirtine, had no consistent effects in acute pain models, it was broadly active in chronic and neuropathic pain models, including capsaicin-induced visceral pain in mice [17], acid-induced muscle allodynia in rats [18], mechanical allodynia and thermal hyperalgesia in nerve-ligated rats [15,19], and pinprick hypersensitivity in the chronic constriction injury and spared-nerve models in rats [20]. The effective doses of retigabine in pain are similar to those in seizure models, ranging from 5 to 20 mg/kg orally (rats) and up to 10 mg/kg i.p. (rats and mice). The M-channel blockers linopirdine and XE-991 reversed the effects of retigabine on chronic/neuropathic pain [15,19,21].

As with various other AEDs, potential therapeutic uses of retigabine may extend to psychiatric and neuromuscular disorders. Unconditioned anxiety in the marble-burying and elevated zero maze tests showed dose-dependent anxiolytic properties of retigabine (3–10 mg/kg i.p.) in mice [22]. Retigabine (1–4 mg/kg i.p.) also dose-dependently attenuated hyperactivity in the amphetamine and chlordiazepoxide rat model of mania [23]. When administered to rats in combination with addictive psychostimulants, retigabine (1–10 mg/kg i.p.) blocked hyperlocomotion and neuronal activation in key dopaminergic systems, suggesting that it may interfere with the reinforcing effects of these drugs and be possibly useful in counteracting addiction [24]. In rodent models of primary paroxysmal dystonia and levodopa-induced dyskinesia after striatal dopamine depletion, retigabine and flupirtine dose-dependently reduced dystonia and dyskinesia, effects that were blocked by XE-991 [25,26].

Mechanisms of action

Early investigations showed that retigabine activated a voltage-sensitive, neuronal-specific outward potassium current that was later identified as the M-current that is mediated by KCNQ (Kv7) channels [27,28]. The M-current is characterized by slow activation at low thresholds (–40 to 50 mV), slow deactivation and lack of inactivation [29]. Upon activation by excitatory input, the M-current opposes subsequent depolarizing inputs, precluding escalation of a single spike to a sustained burst discharge [30,31]. The importance of the M-current in regulating neuronal excitability is underscored by the proconvulsant effects of the M-current blocker linopirdine [32] and the association between benign familial neonatal convulsions and loss-of-function mutations in *KCNQ2* and *KCNQ3* genes [33].

The M-current and KCNQ2, KCNQ3, KCNQ4 and KCNQ5 potassium channel subunits are found throughout the nervous system, and they are enriched in areas associated with oscillation and synchronization [34]. KCNQ channel subunits comprise six transmembrane domains and a large intracellular C-terminus (Fig. 50.1) [35]. An association domain in the C-terminus directs four subunits to co-assemble, forming a pore lined by the fifth and sixth transmembrane segments of each subunit. Functional channels can be formed by homomeric KCNQ2, KCNQ4 and KCNQ5, although they preferentially form higher-conducting heteromers in the presence of KCNQ3 [27,29,36]. The classical M-current in sympathetic neurones most closely resembles the current through heteromers of KCNQ2 and KCNQ3 subunits (KCNQ2/3) [29], while the M-currents in sensory outer hair cells of the cochlea [37] and in axons of large myelinated fibres of the sciatic nerve [38] are apparently carried by homomers of KCNQ4 and KCNQ2, respectively. Subunits KCNQ2, KCNQ3 and sometimes KCNQ5 are co-localized in many areas of the central nervous system (CNS) [16,36]. The precise nature of M-currents in many neuronal populations has yet to be elucidated.

In the presence of retigabine, the M-current activates at a lower threshold, closer to the resting membrane potential, and its amplitude is augmented at negative potentials [27,28,39]. Retigabine enhances the M-current by increasing the channel open probability, accelerating activation and slowing deactivation, without altering single-channel conductance or channel density [40,41]. A putative high-affinity binding site has been identified in the ion pore region that requires at least a tryptophan on the fifth transmembrane segment and a glycine on the sixth transmembrane segment [42,43]. Binding of retigabine to this site appears to alter the channel gating mechanism, lowering the energy required for channel opening (Fig. 50.2).

Enhancement of the M-current by retigabine is voltage and concentration dependent and specific for subunits KCNQ2–5 [40,44]. At concentrations as low as 0.1 μmol/L, retigabine shifts the voltage-dependent activity of KCNQ2–5 channels expressed in cultured cells to more negative potentials; maximal enhancement is achieved with 10 μmol/L retigabine [41]. In contrast, retigabine is a weak inhibitor (IC_{50} = 100 μmol/L) of the predominantly cardiac KCNQ1 channels. Homomeric KCNQ3 channels, although weakly expressed on the cell surface and probably not responsible for endogenous M-current, show the greatest responsiveness to retigabine (EC_{50} = 0.9 μmol/L), followed by KCNQ2/3 (EC_{50} = 1.9 μmol/L) and KCNQ2 (EC_{50} = 2.5 μmol/L) [40]. Retigabine has comparable potency at KCNQ3/5 heteromers, but has less pronounced effects on KCNQ4 [40,44]. Consistent with the potency of retigabine in exogenously expressed KCNQ channels, 0.1–10 μmol/L retigabine activates endogenous M-currents, as

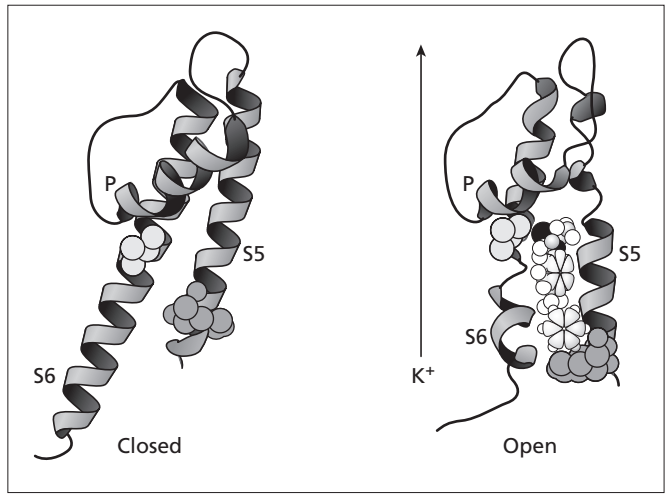

Fig. 50.2 Ribbon schematic of KCNQ2 channel subunit fifth (S5) and sixth (S6) transmembrane domains and P-loop (P), comprising the selectivity filter, pore and gate. Retigabine binds near the gate, favouring channel opening and the outward flow of potassium ions. Adapted from ref. 42.

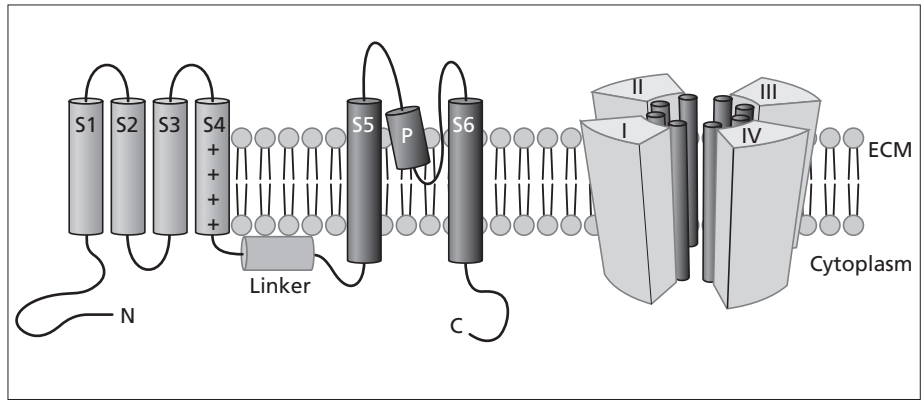

Fig. 50.1 Schematic illustration of a KCNQ2–5 channel subunit (left) comprising six transmembrane domains (S1–6), a P-loop (P), and intracellular termini. S4 detects voltage, S5–P–S6 line the pore. Functional channels are formed by the interaction of four subunits (right). Adapted from ref. 35.

demonstrated in neurones dissociated from sympathetic ganglia [45] and hippocampus [46], dopaminergic neurones in midbrain slices [47], and CA1 pyramidal neurones in hippocampal slices [31,48,49]. Importantly, initial firing of action potentials is not affected by retigabine in these neurones, but subsequent bursting is strongly attenuated (Fig. 50.3). Thus, epileptiform activity induced by electrical stimulation [50] or various bath manipulations (4-aminopyridine [51,52], low Ca^{2+} [19], or low Mg^{2+} [53,54]) in brain slices is suppressed in the presence of 1–100 μmol/L retigabine.

The dampening of neuronal hyperexcitability by retigabine is reversed by antibodies against KCNQ2 channels [55], and by the direct M-current antagonists linopirdine and/or XE-991 [47,48,56,57], arguing for a primary role of M-current enhancement in the pharmacological activity of retigabine.

No retigabine binding interactions were observed in a broad panel screen of known modulator sites on neural receptors, enzymes or second-messenger systems [2]. At concentrations up to 100 μmol/L, retigabine did not interact with the benzodiazepine and GABA binding sites on the $GABA_A$ receptor, or the glutamate, glycine and ion channel binding sites of the NMDA receptor complex. Likewise, currents through NMDA, AMPA or kainate glutamate receptors are not directly affected by retigabine. Early suggestions that retigabine could alter the synthesis of excitatory amino acids [58] or GABA [59] have not been substantiated [34]. At concentrations (≥10 μmol/L) exceeding those achieved with therapeutic dosages (2–6 μmol/L with 600–1200 mg/day), retigabine potentiated GABA-evoked chloride currents at a non-benzodiazepine site in cultured neocortical neurones [60] and isolated $GABA_A$ receptor complexes [61]. However, a GABAergic effect was lacking in limbic slices [50] or isolated $GABA_A$ receptors from hippocampal pyramidal neurones [62], obscuring the contribution of GABA to the seizure-suppressing action of retigabine.

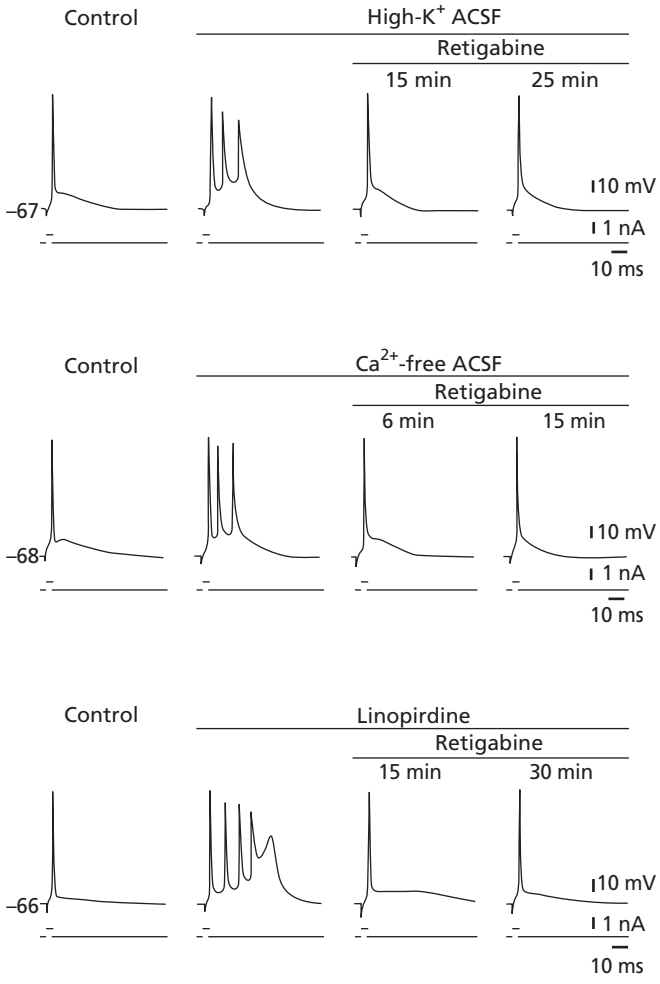

Fig. 50.3 Under excitatory bath conditions, CA1 neurones in hippocampal slices respond to stimulation with bursts of action potentials. Treatment with 10 μmol/L retigabine blocks bursting without affecting the initial spike. Adapted from ref. 31.

Toxicology data

In general, the across-species acute toxicity of retigabine was limited to CNS effects, such as hyperkinesia, hypokinesia, disturbed coordination, stilted gait, tremor and convulsions [2]. In repeated-dose studies in rodents and, to a lesser extent, in dogs, retigabine administration was associated with bladder and minor renal changes. These may have reflected inhibition of bladder contractility and urinary retention secondary to the effects of retigabine on KCNQ channels in the muscle of the bladder [63]. Retigabine did not prolong QTc interval in isolated guinea pig hearts and had no effect on ECG parameters monitored continuously in dogs receiving oral doses of up to 38 mg/kg for 7 days.

No retigabine-related effects on reproductive function were observed in male or female rats [2]. No teratogenic effects of retigabine were detected in rats and rabbits at a dose of 60.0 mg/kg orally. Perinatal/postnatal administration of retigabine to mated female rats was not associated with developmental toxicity in offspring except delayed growth at the highest dose level (61.9 mg/kg orally). Evaluation of retigabine safety in juvenile rats is ongoing. Retigabine is not mutagenic or carcinogenic [2].

Pharmacokinetics

Absorption

Retigabine is rapidly absorbed from the gastrointestinal tract, with peak serum concentrations (C_{max}) achieved within 0.6–1.5 h following single (25–600 mg) or multiple doses (100–300 mg twice daily) in healthy volunteers [64]. A similar profile is observed at steady state in patients with epilepsy receiving 100–1200 mg/day (twice or three times daily administration), with exposure (area under the plasma concentration–time curve) increasing in proportion to retigabine dose. Over the therapeutic dosage range of 600–1200 mg/day, the average retigabine concentration with three times daily administration is 0.6–1.2 μg/mL, fluctuating from a peak (C_{max}) of 0.8–2.0 μg/mL to trough concentrations of 0.5–1.0 μg/mL.

The bioavailability (F) of orally administered retigabine is about 60% compared with an intravenous dose, primarily due to first-pass metabolism [2]. When retigabine is taken with a high-fat

meal, C_{max} is modestly increased compared with administration in the fasted state, but exposure is not changed, demonstrating that retigabine can be taken without regard to food [2].

Distribution

The volume of distribution at steady state of retigabine, calculated after intravenous dosing, is about 2–3 L/kg.

The binding of retigabine to plasma proteins is about 80%. Plasma protein binding is reversible and independent of plasma concentration (0.1–2.0 μg/mL).

Metabolism and elimination

Retigabine is cleared partly by renal excretion in unchanged form and partly by metabolic elimination. About 20–30% of an orally administered radiolabelled dose is recovered in the urine as unchanged parent drug, and another 50–65% as metabolites.

Retigabine does not appear to be a substrate of oxidative cytochrome P450 (CYP) isozymes. Metabolism is almost exclusively by hydrolysis/*N*-acetylation and glucuronidation [65]. A major metabolite in humans is an *N*-acetyl derivative that has weak pharmacological effects and inconsistent antiseizure activity in preclinical models. Uridine diphosphate glucuronosyltransferase isozymes (UGT1A1, A3, A4, A9) metabolize retigabine and the *N*-acetyl metabolite by glucuronidation at the *N*2 and *N*4 amino groups [66,67].

The half-life of retigabine and its *N*-acetyl metabolite is about 8–10 h on average [64]. The apparent oral clearance (CL/*F*) is in the order of 0.5–0.7 L/h/kg. Retigabine does not induce or inhibit its own metabolism and pharmacokinetic profiles after multiple dose (15 days) can be predicted from single-dose pharmacokinetics.

Pharmacokinetics in special populations

Several *in vitro* and *in vivo* studies have examined the effects of impaired glucuronidation and/or impaired acetylation on retigabine metabolism. Preparations of kidney microsomes, which lack UGT1A1, and hepatic microsomes with a loss-of-function mutation in the *UGT1A* gene (sampled from individuals with Crigler–Najjar type II syndrome) still produced glucuronide conjugates of retigabine [66]. In individuals with genetic polymorphisms in drug-metabolizing enzymes, the pharmacokinetics of retigabine was not altered by polymorphisms that impair UGT1A1 glucuronidation (Gilbert's syndrome) or result in slow acetylation by *N*-acetyltransferase 2 (NAT2) [68]. Taken together, these studies suggest the existence of alternative routes of retigabine metabolism and glucuronidation that may involve other UGT1 or UGT2 isozymes, as well as extrahepatic metabolism. Dose adjustments are not required in individuals who are slow acetylators or have glucuronidation polymorphisms.

A study in healthy young volunteers (18–40 years) and older subjects (66–81 years) evaluated the effect of old age and gender on the pharmacokinetics of retigabine administered as a single 200-mg dose [69]. Weight-normalized clearance did not differ according to gender. However, retigabine was eliminated more slowly in older than in younger subjects, resulting in 42% higher mean exposure and 30% longer half-life. Based on a pharmacokinetic study showing that retigabine clearance and exposure are influenced by renal impairment, age-related differences in clearance are likely to reflect at least in part age-related differences in renal function.

Relative to healthy individuals, retigabine exposure increased by about 30% in patients with mild renal impairment (creatinine clearance, 50–80 mL/min) and by about 100% in patients with moderate (30 to < 50 mL/min) to severe (<30 mL/min) renal impairment or end-stage renal disease requiring dialysis [2].

Retigabine exposure is also increased in individuals with moderate (Child–Pugh score, 7–9) or severe (Child–Pugh score >9) hepatic impairment. Whereas mild hepatic impairment did not alter the pharmacokinetics of a single 100-mg dose of retigabine, moderate and severe hepatic impairment resulted in 50% and 100% higher exposure, respectively [2].

Population pharmacokinetic analysis of data from healthy volunteers and patients with epilepsy identified body surface area, age and creatinine clearance as co-variates having meaningful effects on retigabine pharmacokinetics.

Drug interactions

Effect of other drugs on retigabine pharmacokinetics

Studies *in vitro*

In human liver microsomal assays, neither lamotrigine nor imipramine affected retigabine glucuronidation by human liver microsomes, even at very high concentrations [66]. Because valproic acid inhibited retigabine glucuronidation with K_i values of ≥3.5 mmol/L, which are five or more times the therapeutic concentrations of valproic acid, a clinically relevant effect of valproic acid on retigabine pharmacokinetics was considered unlikely.

Studies *in vivo*

In healthy volunteers (n = 15), phenobarbital (90 mg/day for 28 days) did not alter the pharmacokinetics of retigabine (200 mg three times a day) [70] even though phenobarbital induces UGT1A1 and increases the clearance of other AEDs metabolized by *N*′-glucuronidation, such as lamotrigine.

In a separate study in healthy volunteers (n = 14), administration of a very low dose of lamotrigine (25 mg/day for 6 days) did not affect the pharmacokinetics of a single 200-mg dose of retigabine [71].

In a study designed to evaluate pharmacokinetics of retigabine as adjunctive therapy and as monotherapy in patients with epilepsy, retigabine clearance (CL/*F*) was increased by 36% and 27%, respectively, in patients co-medicated with the enzyme-inducing AEDs phenytoin (n = 9) and carbamazepine (n = 8). Neither valproic acid (n = 4) nor topiramate (n = 5) significantly altered retigabine pharmacokinetics. In contrast, population pharmacokinetic analysis of data from all clinical studies involving more than 800 patients did not identify any effect of enzyme-inducing AEDs or clinically meaningful effects of non-enzyme-inducing AEDs on retigabine pharmacokinetics.

Effect of retigabine on pharmacokinetics of other drugs

Studies *in vitro*

In human liver microsome preparations, retigabine had only a modest potential to inhibit the CYP isozyme CYP2A6 (IC_{50} = 7.6 μg/mL), and low or no potential to inhibit other tested CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A9/11; IC_{50} > 33 μg/mL) at concentrations expected to reflect C_{max} in patients receiving therapeutic doses (up to 2.0 μg/mL). Based on these findings, it was considered unlikely that retigabine can alter the pharmacokinetics of drugs that are metabolized by CYP isozymes.

Studies *in vivo*

In a study conducted in 15 healthy volunteers, treatment with retigabine at a dosage of 600 mg/day for 15 days was associated with a mean 22% increase in the clearance (CL/*F*) of a single 200-mg dose of lamotrigine [71].

In phase III studies, retigabine co-administration was not associated with clinically meaningful changes in the trough concentrations of concomitant AEDs, with the exception of a 20% reduction in trough lamotrigine concentrations, as in the study conducted in healthy subjects. Because of its modest magnitude, the interaction of retigabine with lamotrigine is unlikely to be clinically significant in the majority of patients.

The potential for an interaction between retigabine (750 mg/day for 19 days after a 9-day titration period) and an oral contraceptive preparation (0.035 mg ethinylestradiol + 1 mg norethindrone) has been evaluated in healthy female volunteers. No change in ethinylestradiol exposure was observed, whereas norethindrone exposure was increased by 28%. These findings suggest no potential for reduced contraceptive efficacy when retigabine is added on to oral contraceptive hormones. Although the study was not designed to assess the effect of oral contraceptives on retigabine, retigabine exposure was similar to that in other studies, suggesting that contraceptive hormones do not markedly alter retigabine pharmacokinetics.

Serum level monitoring

There is insufficient information on the value of monitoring serum retigabine levels, and there is no indication that monitoring serum retigabine concentrations may help in individualizing therapy, except for compliance assessment.

Efficacy

Studies in patients with epilepsy

In initial exploratory, open-label studies, adjunctive therapy with retigabine (300–1200 mg/day) in patients with inadequately controlled seizures was associated with a median reduction in seizure frequency by approximately 40%. These early clinical observations have been confirmed in a series of randomized double-blind, placebo-controlled trials and long-term open-label extension studies in adults with partial-onset seizures.

The first such study was a dose-ranging trial (Study 205 [72]) evaluating 600, 900 and 1200 mg/day retigabine administered three times a day versus placebo as adjunctive therapy. The intent-to-treat (ITT) study population comprised 396 adults of 16–70 years of age with a baseline monthly seizure frequency of four or more partial-onset seizures, with or without secondary generalization, despite stable therapy with one or two AEDs. After an 8-week prospective observation to document baseline seizure frequency, patients were randomized to placebo or 600, 900 or 1200 mg/day retigabine for the 16-week double-blind treatment period. The starting dose was 300 mg/day (100 mg three times a day), and titration proceeded with weekly dose increments of 150 mg/day (50 mg three times a day) over 6 weeks to the assigned target dosage. Only two 100-mg dose decrements were allowed during weeks 7 and 8; minimum dosages during the 8-week maintenance phase were 400, 700 and 1000 mg/day.

Patients in Study 205 were on average 35–38 years of age, their mean duration of epilepsy was approximately 20 years, and their median baseline seizure frequency was 8 to 10 seizures per month. In the majority (70%) of patients, retigabine was added to two other AEDs. Median seizure frequency was reduced by 23%, 29% and 35% from baseline in the groups assigned to 600, 900 and 1200 mg/day retigabine, respectively, compared with a 13% reduction in the placebo group ($P < 0.001$ for dose-dependent response across treatment arms). Responder rates (proportions of patients with ≥50% seizure reduction) were 16% with placebo and 23%, 32% and 33% with 600, 900 and 1200 mg/day retigabine, respectively (900 and 1200 mg/day versus placebo, $P < 0.05$). Of patients completing double-blind treatment, 80% (222/279) enrolled in a long-term open-label extension. During the blinded transition, patients in the placebo and 600-mg retigabine arms were up-titrated and those in the 1200-mg arm were down-titrated to a target dosage of 900 mg/day. Patients initially assigned to the 900-mg group remained at the dosage administered during the double-blind maintenance phase. During the long-term extension, dosages of retigabine and concomitant AEDs could be adjusted according to clinical need. Of those entering the open-label extension (mean duration of follow-up, 353 days), 26% discontinued due to inadequate seizure control and 9% discontinued due to adverse events [2]. The 1-year retention rate was 55%. At the end of open-label treatment, 78% were receiving ≤900 mg/day and the optimized dose was ≥1200 mg/day in only 10% of patients (maximum dosage, 1500 mg/day). During open-label treatment, seizure control improved in the groups initially assigned to the placebo or 600-mg retigabine arms and was maintained in those initially assigned to the 900- or 1200-mg retigabine arms. The overall responder rate was 46%. The 6-month and 12-month seizure-free rates were 9% and 6%, respectively. No additional AEDs were added in those who were seizure free.

The results of the dose-ranging trial have been validated by two separate double-blind, placebo-controlled adjunctive therapy studies that evaluated three retigabine dosages (1200 mg/day in RESTORE 1/Study 301; 600 or 900 mg/day in RESTORE 2/Study 302). In both studies, the starting dosage of 300 mg/day was increased weekly in 150 mg/day increments and the maintenance period was 12 weeks. Treatments were administered three times a day in both studies. Dosage reductions were not allowed

in Study 302. In Study 301, dosage could be reduced to 1050 mg/day at week 7 and continued for the remainder of the maintenance phase. Patients who could not achieve target dosages were withdrawn. Patients were adults (18–75 years of age) with documented refractory partial-onset seizures, refractoriness being defined as ≥2 years since epilepsy diagnosis and past failure of two or more approved AEDs, alone or together, in adequate doses for a sufficient period of time to evaluate clinical response. Patients were required to have four or more seizures per month during the 8-week prospective baseline.

Patient characteristics at baseline were very similar across the two studies. Patients had been diagnosed with epilepsy 22–24 years before study entry, had failed three to four (median) AEDs in the 3 years prior to study entry, and were having 11 to 12 (median) seizures per month. More than 75% of patients were receiving two or three AEDs. Mean age was 37–38 years and 52–54% were female. The ITT populations comprised 538 patients in RESTORE 2/Study 302 (placebo, $n = 179$; 600 mg, $n = 181$; 900 mg, $n = 178$) and 305 patients in RESTORE 1/Study 301 (placebo, $n = 152$; 1200 mg, $n = 153$). During double-blind treatment, retigabine at all three doses significantly reduced median seizure frequency compared with placebo (Table 50.1). Efficacy was clearly dose related in terms of both seizure frequency reduction and responder rate, as well as in the proportion of patients seizure free once the target doses were achieved. In patients completing titration, 3% (5/158) in the 600-mg group, 5% (7/149) in the 900-mg group, and 8% (9/119) in the 1200-mg group were seizure free during the 12-week maintenance period, compared with 1% (4/301) in the placebo group. Improved seizure control favouring retigabine over placebo emerged within the first 2 weeks of titration, and within 3 weeks of initiating retigabine therapy, the difference was statistically significant ($P = 0.002$).

Patients completing double-blind treatment in Studies 301 and 302 were eligible for continued retigabine treatment in open-label extensions, which are ongoing. Interim analysis suggests that efficacy is being maintained at the levels achieved during the maintenance phase of the initial double-blind studies.

Table 50.1 Efficacy results from phase III double-blind placebo-controlled adjunctive therapy trials of 600, 900 and 1200 mg/day retigabine in patients with refractory partial-onset seizures. Results refer to ITT analysis from ref. 2.

	RESTORE 2 (Study 302)			RESTORE 1 (Study 301)	
	Placebo	Retigabine 600 mg/day	Retigabine 900 mg/day	Placebo	Retigabine 1200 mg/day
Median percentage seizure reduction					
Overall	15.9%	27.9%	39.9%	17.5%	44.3%
P-value		<0.01	<0.001		<0.001
Titration	11.0%	26.1%	32.1%	10.4%	30.4%
P-value		<0.01	<0.001		<0.001
Maintenance	17.4%	35.3%	44.3%	18.9%	54.5%
P-value		<0.01	<0.001		<0.001
Responder rate (>50% reduction in baseline seizure frequency)					
Overall	17.3%	31.5%	39.3%	18.0%	45.0%
P-value		<0.01	<0.001		<0.001
Titration	17.3%	28.7%	33.1%	17.3%	37.7%
P-value		<0.01	<0.001		<0.001
Maintenance	18.9%	38.6%	47.0%	23.2%	55.5%
P-value		<0.01	<0.001		<0.001

Studies in patients with other disorders

To date, retigabine has been evaluated clinically in two disorders other than epilepsy. One pilot open-label study ($n = 10$) reported positive effects of retigabine monotherapy (600–1200 mg/day) in some patients with prolonged mania who had not responded to antipsychotic or mood-stabilizing drugs [73]. In addition, a double-blind, placebo-controlled proof-of-concept study has been initiated in patients with postherpetic neuralgia.

Adverse effects

Consistent with AEDs as a class, the most common adverse events associated with retigabine are non-specific CNS effects such as dizziness, somnolence and fatigue (Table 50.2), which are usually mild to moderate in nature. The temporal pattern of these events suggests that peak-dose effects may contribute to the tolerability profile. Among non-CNS events, a small increased incidence of bladder-related adverse events (e.g. urinary hesitancy) relative to placebo was observed with retigabine. Significant urinary retention was observed rarely and occurred at similar frequencies in the retigabine and placebo groups. Bladder ultrasound revealed a small increase in mean post-void residual volume at the 1200-mg dose but not at lower doses, a finding that is of uncertain clinical significance. Other clinical and laboratory monitoring, including ECG, urinalysis and vital signs, showed no clinically significant changes related to retigabine administration during double-blind, placebo-controlled trials or long-term, open-label treatment, with the exception of occasional transient transaminase elevations and modest, dose-related weight gain that generally reached a plateau during open-label treatment [2].

Based on double-blind, placebo-controlled trials, which featured forced titration and very little dosing flexibility to reduce

Table 50.2 Most common (>10% in any treatment group) adverse events (%) recorded in phase III double-blind placebo-controlled adjunctive therapy trials of 600, 900 and 1200 mg/day retigabine in patients with refractory partial-onset seizures.

	Placebo ($n = 331$)	Retigabine (mg/day)		
		600 ($n = 181$)	900 ($n = 178$)	1200 ($n = 153$)
Dizziness	9	17	26	40
Somnolence	13	14	26	31
Fatigue	5	17	15	16
Confusion	1	2	5	14
Dysarthria	1	5	2	12
Headache	16	11	17	12
Ataxia/gait disturbance	4	3	5	12
Urinary tract infection	5	1	2	12
Tremor	3	2	8	11
Vision blurred	2	1	5	11
Nausea	5	6	7	11

From ref. 2 with permission.

common treatment-emergent adverse events, the tolerability of retigabine is primarily dose related and influenced by titration or dose management. In phase III trials, discontinuation rates due to adverse events were 14% at 600 mg/day, 26% at 900 mg/day, and 27% at 1200 mg/day, compared with 8% among patients assigned to placebo. More than two-thirds of discontinuations occurred during forced titration. The most common adverse events associated with retigabine discontinuation were dizziness (6%), fatigue (4%), somnolence (4%) and confusion (3%).

Therapeutic potential

Clinical studies have documented the efficacy of retigabine as adjunctive therapy in adults with refractory partial-onset seizures. Because retigabine is unique among AEDs in targeting M-current KCNQ channels and thereby dampening neuronal excitability, its therapeutic potential may extend more broadly to use in relatively early stages of the medical management of localization-related epilepsies, for example when sodium channel blockers (such as carbamazepine) have failed. Although the possibility exists that retigabine may also be of value in the treatment of generalized epilepsies, and preclinical data suggest a potential for efficacy in non-epilepsy disorders such as pain and mood disorders, such therapeutic uses have not yet been validated in controlled clinical studies.

Double-blind, placebo-controlled studies as well as open-label, long-term studies suggest that the optimal dosage for many patients will be 600–900 mg/day. Based on open-label studies when dosages of retigabine could be adjusted according to clinical response, perhaps 20% of patients will require dosages up to 1200 mg/day. Due to reduction in retigabine clearance in individuals with renal impairment or moderate to severe hepatic impairment, clinicians should be cautious with dose escalation and target doses in these patients.

The tolerability of retigabine is influenced by titration rate and by dose frequency. Dose management techniques applied to other AEDs may be useful in the management of patients receiving retigabine. In particular, retigabine should be initiated gradually, for example with a starting dose of 300 mg/day, which can be increased weekly in 150-mg increments. In clinical trials, retigabine was administered in three divided doses to help reduce peak-dose effects (e.g. dizziness) similar to those seen with immediate-release formulations of other AEDs with relatively short half-lives.

Because retigabine is associated with a relatively low potential for pharmacokinetic interactions with other commonly administered drugs, dosage adjustments of other AEDs are not required when retigabine is added, although clinicians should be aware that lamotrigine levels may decrease by about 20% on average. However, increasing the number of AEDs in a therapeutic regimen increases the potential for pharmacodynamic interactions that may adversely affect tolerability. If adverse effects emerge with the addition of retigabine, consideration should be given to reducing the dosages of concomitant AEDs.

Safety of retigabine during pregnancy or lactation in humans has not been established. As with all AEDs, retigabine should be used during pregnancy or by nursing women only if the potential benefit outweighs the potential risk for the fetus or the infant. Retigabine does not alter the pharmacokinetics of contraceptive hormones.

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51 Rufinamide

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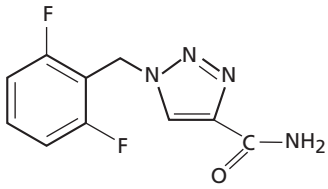

Primary indications	Adjunctive therapy of Lennox–Gastaut syndrome (>4 years of age) and partial-onset seizures
Usual preparation	Tablets: 100, 200 and 400 mg
Usual dosages	Patients weighing <30 kg: 200–1000 mg/day (200–600 with valproic acid co-medication); 400–1800 mg/day, 400–2400 mg/day and 400–3200 mg/day for patients weighing 30–50 kg, >50–70 kg and >70 kg, respectively. Higher doses have been used, up to 4800 mg/day
Dosing frequency	Twice daily
Significant drug interactions	Phenobarbital, carbamazepine, phenytoin, primidone and vigabatrin may cause a slight to moderate decrease in serum rufinamide levels. Valproic acid increases serum rufinamide levels. Rufinamide may slightly decrease the serum levels of carbamazepine and lamotrigine, and increase slightly those of phenytoin and phenobarbital. Rufinamide decreases the serum levels of oral contraceptive steroids and triazolam
Serum level monitoring	There is insufficient information on the value of monitoring serum rufinamide levels
Target range	Not clearly defined
Common/important side-effects	Dizziness, headache, nausea, somnolence, diplopia, blurred vision, fatigue and ataxia
Main advantages	Robust efficacy in the Lennox–Gastaut syndrome trial
Main disadvantages	Modest efficacy in partial-onset seizures
Mechanism of action	Limits excessive firing of sodium channel-dependent action potentials
Oral bioavailability	Up to 85% in the fed state, but decreases with increasing dosage within the clinically used dose range. Bioavailability increases by about 40% when the drug is taken with food
Time to peak levels	4–6 h
Elimination	Primarily by hydrolysis of the carboxamide group
Volume of distribution	0.8 L/kg at 3200 mg/day, assuming complete oral bioavailability. Increases with increasing dosage, because actual bioavailability decreases as dose is increased
Elimination of half-life	8–12 h (shorter in patients co-medicated with enzyme inducers)
Plasma clearance	About 90 mL/h/kg in adults, at a dosage of 45 mg/kg. Increases with increasing dosage, and is higher in children than in adults
Protein binding	30%
Active metabolites	None
Comment	A potentially valuable drug, but more data are needed to define its role in current therapy

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Introduction

Rufinamide is a novel antiepileptic drug (AED) that is structurally unrelated to any currently marketed anticonvulsant. The European Medicines Agency (EMEA) approved the drug on 16 January 2008 for use as an adjunctive treatment for patients 4 years of age and older with Lennox–Gastaut syndrome. The trade name of rufinamide in Europe is Inovelon®.

In 2005, Eisai Company Ltd filed a new drug application with the USA Food and Drug Administration (FDA) seeking approval for rufinamide as an adjunctive therapy for focal epilepsy with and without secondary generalization in patients 12 years of age and older, and also as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in patients 4 years of age and older. Trade name rights have been reserved in the USA for the name 'Inavra'.

Development of rufinamide was started by Ciba-Geigy in Switzerland in the 1980s. The drug, then called CGP-33101, initially underwent preliminary assessment for anticonvulsant activity at the USA National Institute of Health (Rockville, MD) and at Ciba-Geigy. After Ciba-Geigy merged with Sandoz and changed its name to Novartis, global development of the compound, which was renamed RUF-331, continued. Phase II and III studies conducted in Japan, Switzerland, the USA and other countries were completed by 2001 [1,2]. In February 2004, Eisai Company Ltd acquired the rights to develop rufinamide for epilepsy from Novartis, and the drug is now being developed by Eisai under the name of E2080.

Efficacy studies of rufinamide in epilepsy have had mixed outcomes. Of two monotherapy trials in adults with partial-onset seizures, one was positive and the other did not meet the primary endpoint. In a trial in Lennox–Gastaut syndrome, a large effect size was demonstrated. In addition, there has been a negative trial in patients with primary generalized tonic–clonic seizures and another negative trial in the add-on setting in paediatric patients with partial-onset seizures. A pilot trial in patients with diabetic neuropathic pain was negative but demonstrated a small effect size. A large-scale study in patients with partial-onset seizures is currently ongoing.

Chemistry

Rufinamide, or 1-(2,6-difluorophenyl)methyl-1H-1,2,3-triazole-4-carboxamide, is a white, odourless and slightly bitter crystalline substance. Rufinamide has a low solubility in water and a limited solubility in 0.1 N hydrochloric acid (63 mg/L) and simulated intestinal fluid (59 mg/L). Rufinamide has a chemical formula of $C_{10}H_8F_2N_4O$, which corresponds to a molecular weight of 238.20. It is available as 100-, 200- and 400-mg film-coated tablets. The drug does not show any hygroscopicity; no water was absorbed by the drug when placed in an environment of up to 100% relative humidity. Its provisional shelf-life is 3 years and it requires storage below 30°C [3].

Pharmacology

Activity in experimental models of seizures and epilepsy

The activity profile of rufinamide in experimental models has been studied mainly through the National Institutes of Health (NIH) anticonvulsant drug development programme and at Novartis.

In the maximal electroshock test, which is known to identify AEDs with the potential to suppress generalized tonic–clonic seizures and, in part, partial seizures, rufinamide demonstrated protective activity in rats and mice with an ED_{50} of 6–24 mg/kg per os (orally, p.o.). Oral and intraperitoneal (i.p.) rufinamide potently suppressed maximal electroshock seizure (MES)-induced tonic–clonic seizures (with ED_{50} values of 23.9 and 15.5 mg/kg, respectively) and pentylenetetrazole (PTZ)-induced clonic seizures (with ED_{50} values of 45.8 and 54.0 mg/kg, respectively) in mice [1,3–6].

Repeated dosing for 5 days at a single dose of 6 mg/kg orally did not induce tolerance to the anticonvulsant effects of rufinamide. The anticonvulsant effect in the maximal electroshock test was maintained for 4 h in mice and 8 h in rats [7–9].

In the PTZ test in mice, which is considered a model of clonic seizures and may correlate with activity against absence seizures, rufinamide had an ED_{50} of 300 mg/kg (with a protection rate of 60%). In the subcutaneous PTZ test in mice, oral administration of rufinamide resulted in an ED_{50} of 458 mg/kg. When PTZ was given intraperitoneally, the ED_{50} of rufinamide was higher at 300 mg/kg p.o. indicating lower potency than in the maximal electroshock test [7,10]. Rufinamide was effective in blocking clonic seizures induced in mice by subcutaneous administration of the GABA antagonists bicuculline and picrotoxin, with ED_{50} values of 50.5 and 76.3 mg/kg p.o., respectively. Rufinamide, however, was hardly effective in the glycine inhibition seizures provoked by strychnine.

Rufinamide (at oral doses of 100–300 mg/kg) was effective in delaying the development of kindling and in suppressing afterdischarges in amygdala-kindled cats with generalized tonic–clonic convulsions [1,2,3,5,8,10]. It has also shown effectiveness in reducing seizure frequency in rhesus monkeys with chronic alumina foci in the motor cortex. Hippocampal and cortical afterdischarges induced by electrical stimulation in non-kindled cats are also inhibited by rufinamide.

In most animal models the therapeutic index of rufinamide was generally higher than that of other commonly used AEDs [8].

Mechanism of action

Although the precise mechanisms of action by rufinamide are incompletely known, based on *in vitro* studies the principal mechanism of rufinamide's antiepileptic activity appears to involve modulation of the activity of sodium channels, mainly via prolongation of the inactive state of the channel [1,6]. An additional potential mechanism is represented by inhibition of responses at the glutamate receptor subtype mguR5, which is observed at high concentrations (60% inhibition of quisqualate-induced phosphoinositol turnover at 100 μmol/L concentrations) [8].

The interaction of rufinamide with various neurotransmitters has been investigated. Rufinamide at 10–100 μmol/L had no effect on radioactive flunitrazepam and GABA receptor binding, nor on adenosine uptake. Rufinamide did not affect the receptor binding of any of the following ligands: prazosin (α_1-adrenergic), clonidine (α_2-adrenergic), dihydroalprenolol (β-adrenergic), 5HT (5HT-1), ketanserin (5HT-2), doxepin, cismethyl-dioxolane (cholinergic muscarinic agonist) and quinuclidinyl benzylate (cholinergic muscarinic antagonist). Rufinamide also did not interact with glutamate receptors including R1, R2, R4 and R5, NMDA,

strychnine-intensive glycine or AMPA/kainate receptors [1–3]. Rufinamide at levels of up to 100 μmol/L has been shown to have no effect on benzodiazepine or GABA receptors.

Pharmacokinetics

Absorption and bioavailability

Rufinamide is relatively slowly absorbed from the gastrointestinal tract with peak plasma concentrations being typically reached within 4–6 h (range 1.5–10 h) after a single dose, irrespective of the formulation used and irrespective of intake with or without food [11]. Many of the early studies used a formulation that had only 50% bioavailability of the currently used commercial formulation.

The absolute bioavailability of the commercial formulation is unknown. In an early study in three healthy adult male volunteers who received single oral doses of 600 mg of radiolabelled rufinamide in gelatin capsules with food, absorption was demonstrated to be at least 85% [12,13].

The absorption of rufinamide appears to be limited by its slow dissolution into gastrointestinal contents [11]. Probably because of this, the bioavailability of the drug is dose dependent and the fraction absorbed decreases with increasing doses, resulting in a non-linear relationship between steady-state plasma concentration and dosage [14,15]. In one study, the ratio between steady-state plasma rufinamide concentration and dose during treatment with a dose of 3600 mg twice daily was approximately one-half of that recorded at a dose of 400 mg twice daily [11].

Food also has a significant impact on rufinamide bioavailability [3,16,17]. In single-dose studies, the area under the rufinamide concentration–time curve (area under the curve, AUC) increased by about 30–40% when the drug was ingested with a high-fat meal compared with ingestion in a fasting state [11]. Although an influence of food on rufinamide bioavailability during multiple dosing has not been clearly established, it is recommended that rufinamide always be taken at meal times.

Distribution

The plasma protein binding of rufinamide is low, at about 26–34% [11]. The volume of distribution normalized to a bioavailability of 100% (V_d/F) is in the order of 0.8 L/kg at a dose of 3200 mg/day, but this value is likely to be an overestimate because bioavailability is probably incomplete at that dosage. As expected, larger V_d/F values have been measured in subjects receiving higher dosages, as a result of the dose-dependent decrease in bioavailability [11]. Rufinamide is evenly distributed between erythrocytes and plasma.

The transfer of rufinamide to the embryo was investigated in rats and rabbits after an administration of radioactive rufinamide. The concentrations in the embryo and the amniotic fluid were about a half of those in the maternal blood after 24 h. This transfer was reversible. In rats and rabbits, radioactivity was also identified in the mammary glands with concentrations similar to those in the blood and plasma, suggesting that rufinamide should be excreted with the milk.

Elimination and metabolism

The mean plasma elimination half-life of rufinamide ranges from 8 to 12 h, with an overall mean of about 10 h. Lower values (about 7 h on average) have been determined in patients with epilepsy [11], possibly as a result of induction of rufinamide metabolism by concomitant AEDs. Despite the relatively short half-life, fluctuations in serum rufinamide concentration during a 12-h dosing interval at steady state are relatively moderate, owing to the prolonged absorption phase of the compound.

In population pharmacokinetic modelling of a pooled database drawing from various studies, it was demonstrated that an important factor affecting rufinamide apparent oral clearance (CL/*F*) is body size. There was also a slightly lower clearance in females. This difference, which persisted after adjusting for body size, was not considered clinically significant [18].

In a study designed to evaluate the metabolism and disposition of rufinamide, three adult healthy male volunteers received single oral doses of 600 mg of ^{14}C-labelled microcrystalline rufinamide in gelatin capsules with food. Concentrations of radioactive rufinamide and its metabolites were measured in blood, plasma, urine and faeces. Absorption at this low dose was demonstrated to be at least 85%. The main radioactive compound in plasma was rufinamide. Excretion of drug-related material was largely renal (85%) and was complete (98%) within 7 days. Rufinamide was extensively metabolized, with only 4% recovered unchanged, in urine (2%) and in faeces (2%) [12]. The most prominent metabolite was the carboxylic acid derivative CGP 47292, which was inactive [13]. A few minor metabolites were detected in the urine that appeared to be acylglucuronides of CGP 47292. No other relevant metabolites were detected in the urine and faeces. These results show that biotransformation by hydrolysis is the main mechanism of elimination of rufinamide.

Studies *in vitro* with human liver microsomes provided no evidence for an involvement of cytochrome P450 (CYP) enzymes in rufinamide metabolism and confirmed that the main metabolic pathway is hydrolysis of the carboxamide group, mediated by carboxylesterases, to form CGP 47292 [11]. Carboxylesterases are known to be inducible by agents which induce CYP enzymes, an observation which explains the increase in rufinamide clearance caused by co-medications such as phenytoin and carbamazepine.

Pharmacokinetics in special populations

Children

Only limited data exist on the effect of young age on rufinamide pharmacokinetics. In studies conducted to date, dosage and co-medications varied among age groups and it has been difficult to differentiate the effects of age from those cause by dose-dependent bioavailability and drug–drug interactions.

Sachdeo *et al*. [14] conducted a study to obtain rufinamide safety and pharmacokinetic data in 16 children with epilepsy with an age range of 2–17 years [14,15]. Rufinamide was administered orally in equally divided twice-daily doses of 10 mg/kg/day (week 1) and 30 mg/kg/day (week 2), and at the end of each week blood samples were taken for pharmacokinetic profiling. The data showed a less than dose-proportional increase in serum rufinamide concentrations when the dose was increased from 10 mg/kg/day to 30 mg/kg/day, similar to the data obtained from studies in the adult population. Although no significant differences in pharmacokinetic parameters as a function of age were noted, the small size of the age subgroups makes the data difficult to interpret.

At present, the most informative assessment of the influence of paediatric age on rufinamide pharmacokinetics is provided by a population pharmacokinetic study conducted in patients included in clinical trials. This study suggested that rufinamide CL/*F* is higher in children than in adults receiving similar doses. For example, it was calculated that, at a rufinamide dosage of 45 mg/kg in the absence of interacting co-medications, rufinamide CL/*F* should be in the order of 0.14 L/h/kg in a 4-year-old child weighing 17 kg compared with 0.09 L/h/kg in a man weighing 80 kg.

The elderly

Chang *et al.* [19] evaluated the pharmacokinetics of rufinamide in seven elderly healthy subjects (age range 66–77 years) compared with seven younger gender-matched healthy subjects (age range 18–40 years). This was a single-dose (400 mg) and multiple-dose (400 mg given twice daily for nine doses) open-label parallel group study. The extent of absorption (AUC) and the absorption rates (peak serum concentrations) were similar between the elderly and the young volunteers under both single- and multiple-dose conditions. Elimination half-life values were also similar in the elderly subjects (for single dose 8.6 ± 1.3 h, for multiple dose 8.3 ± 1.1 h) and younger subjects (single dose 10.8 ± 3.2 h, multiple dose 10.2 ± 2.4 h), and were not altered after multiple-dose treatment [20]. Time-independent kinetics was observed in multiple-dose treatment for both the elderly subjects and the younger subjects, as shown by the fact that AUC values during a dosing interval at steady state were similar to $AUC_{0-\infty}$ values after a single dose. These results show that, within the age range explored, rufinamide pharmacokinetics is not altered in the elderly compared with non-elderly adults.

Impaired renal function

A study in patients with severe renal impairment (creatinine clearance of less than 30 mL/min) did not demonstrate any significant difference in rufinamide exposure compared with healthy volunteers after a single 400-mg dose. Haemodialysis, however, when started 3 h after dosing, did reduce rufinamide AUC values by approximately 30%. This might suggest that dialysis can be used to treat patients with toxic levels of the drug.

Impaired liver function

The effect of hepatic impairment on rufinamide pharmacokinetics has not been evaluated.

Drug interactions

Effect of other drugs on rufinamide pharmacokinetics

Using population pharmacokinetic modelling [21–23,11], enzyme inducers, such as carbamazepine, phenytoin and phenobarbital, have been shown to reduce serum rufinamide concentrations. Depending on age and gender, carbamazepine decreased serum rufinamide levels by 19–26% on average; phenobarbital, phenytoin and primidone (assessed together in the model) by 25–46%; and vigabatrin by 14–30% [11]. Valproic acid increased the serum concentration of rufinamide by 12–70% on average, the highest increases being recorded in children, presumably because in the populations included in this analysis serum valproic acid concentrations were higher in children than in adults [11]. In the same analysis, serum rufinamide levels were not affected by lamotrigine or topiramate.

Effect of rufinamide on the pharmacokinetics of other drugs

In an *in vitro* study [16], rufinamide was incubated at concentrations of up to 300 μmol, with various substrates, in human liver microsomal fractions to evaluate any potential inhibitory effect on the activities of various human CYP isoenzymes that are known to be responsible for the metabolism of several drugs. Rufinamide did not demonstrate any inhibition on the activities of these human P450 isoenzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11. This suggests that rufinamide is unlikely to inhibit the biotransfomation of drugs that are metabolized by these enzymes.

Formal pharmacokinetic studies to assess the influence of rufinamide on the disposition of other AEDs have not been conducted. However, the effect of rufinamide on the serum levels of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate and valproic acid has been evaluated using a population pharmacokinetic analysis of measurements made during clinical trials. Rufinamide, at a concentration of 15 μg/mL, was estimated to cause a small decrease in clearance of phenobarbital and phenytoin. This would result, depending on age groups, in a mean increase of 8–13% in the levels of phenobarbital and an increase of 7–21% in the levels of phenytoin. Rufinamide was also estimated to cause a small increase in the clearance of lamotrigine and carbamazepine, which would result in a decrease of 7–13% in the concentration of these drugs [21]. The serum levels of topiramate and valproic acid were not affected by rufinamide in this analysis.

A single-centre open-label cross-over study in 18 healthy female volunteers was conducted to investigate the effects of rufinamide on the metabolism of an oral contraceptive pill [24]. Subjects were maintained on the pill for at least two cycles prior to initiation of the study, and rufinamide 800 mg b.i.d. was taken on days 22–35. During rufinamide administration, the AUC and the C_{max} (peak plasma concentration) of ethinylestradiol decreased by 22% and 31%, respectively, whereas the AUC and C_{max} of norethindrone decreased by 14% and 18%, respectively. These findings suggest that rufinamide stimulates the metabolism of contraceptive steroids by a moderate degree. Whether a greater magnitude of interaction occurs at higher dosages of rufinamide remains to be determined.

In another study, rufinamide, given at the low dose of 800 mg/day for 11 days to 18 healthy subjects, caused a 36% decrease in the serum levels (AUC) of concomitantly taken triazolam. This suggests that rufinamide induces the CYP3A4 enzyme system [11]. Conversely, rufinamide, also at a dose of 800 mg/day, did not influence the pharmacokinetics of olanzapine, a CYP1A2 substrate [11].

Serum level monitoring

A high-performance liquid chromatography (HPLC) method has been developed for the simultaneous determination of the levels of rufinamide and its main carboxylic metabolite (CGP 47292) in blood [25,26].

Pharmacokinetic/pharmacodynamic relationships have been explored as part of a population pharmacokinetic analysis of data

from patients included in clinical trials [11]. This analysis showed a decrease in seizure counts with increasing serum rufinamide concentrations, at least within the concentration ranges encountered in clinical trials. The plasma rufinamide concentration estimated to be associated with a mean 25% reduction in seizure frequency was 13 μg/mL, which is within the range expected to be achieved with the recommended dose range. Mean serum rufinamide concentrations were also higher in patients with adverse effects than in patients not reporting adverse effects.

These data suggest that clinical response to rufinamide is related to the drug's serum concentration. There are, however, insufficient data to determine the value of serum level monitoring in optimizing therapy with this drug.

Efficacy

To date, a total of nine double-blind efficacy studies have been conducted. An additional large-scale adjunctive therapy study for patients with focal epilepsy is currently ongoing. Table 51.1 summarizes the various studies and their outcomes. Of those studies, one was terminated early due to poor enrolment. Of the remaining eight, five were reported to demonstrate rufinamide efficacy compared with the control group and three were negative studies.

Monotherapy studies in patients with partial-onset seizures

A multicentre, double-blind, low-dose, active-control, randomized, parallel-group monotherapy study (Study 0016) compared 300 mg/day with 3200 mg/day rufinamide in patients with refractory partial seizures who were initially on one or two AEDs [27]. Seventy patients were randomized to 300 mg/day and 72 were randomized to 3200 mg/day for up to 112 days. Concomitant AEDs were simultaneously tapered and discontinued over a 42-day period beginning at randomization. Patients were allowed to exit the study by meeting criteria based on seizure frequency or severity, or completing 112 days of treatment. The primary efficacy outcome was the percentage of patients meeting exit criteria. Overall, 66.7% in the high-dose group and 72.5% in the low-dose group met exit criteria, a non-significant difference. The median time to meeting an exit criterion showed a trend favouring the high dose (56 days) over the low dose (32 days), but again the difference was not statistically significant ($P = 0.0968$).

Another double-blind, randomized, placebo-controlled, parallel group study (Study 0038) was conducted in patients with partial seizures who completed inpatient evaluation for epilepsy surgery, and were not on any AED other than low-dose lorazepam [28]. Each patient had to have 2–10 partial seizures during the 48-h baseline phase. After completing this phase, patients were randomized to receive rufinamide ($n = 52$) or placebo ($n = 52$) for the 10 days of the double-blind phase. Rufinamide dose was 2400 mg/day on day 1 and 3200 mg/day on days 2–10, given on a t.i.d. schedule. The patients continued on treatment until they completed 10 days or met one of the exit criteria. The mean daily dose of rufinamide was 2970.7 mg. Rufinamide-treated patients demonstrated a significantly greater median number of days to meet an exit criterion than placebo-treated patients, 4.8 days versus 2.4 days ($P = 0.0499$). Approximately the same percentage of patients in the rufinamide group (67.3%) and in the placebo group (69.2%) met an exit criterion ($P = 0.8809$). The median times to first, second and third partial seizures were significantly longer with rufinamide than with placebo ($P \leq 0.0348$).

The third study (Study 0039) was a multicentre, double-blind, randomized, placebo-controlled, parallel-group monotherapy trial in currently untreated patients with recent onset of partial seizures. Because only 29 patients were randomized, 14 to rufinamide and 15 to placebo, the study was discontinued owing to a lack of enrolment.

Table 51.1 Double-blind placebo-controlled efficacy studies.

Study	Type of epilepsy	Design	Dosage	No. of patients R/P	Outcome
AE-ET1	Partial	Add-on	200–1600 mg	R-514 P-133	Positive
AE-PT2	Partial or Generalized	Add-on	400–1600 mg	R-25 P-25	Positive
0016	Partial	Monotherapy	300–3200 mg	300 mg-70 3200 mg-72	Negative
0018	Generalized	Add-on	800 mg	R-78 P-75	Negative
0021A	Partial	Add-on	3200 mg	R-156 P-157	Positive
0021P	Partial (pediatric)	Add-on	45 mg/kg	R-136 P-132	Negative
0022	LGS	Add-on	45 mg/kg	R-74 P-64	Positive
0038	Partial (in-patient)	Monotherapy	3200 mg	R-52 P-52	Positive
0039	Partial	Monotherapy (new diagnosis)	1200 mg	R-14 P-15	Early termination[a]
E2080-301	Partial	Add-on >12 years old	3200 mg	408 patients planned	On-going

R, rufinamide; P, placebo.
[a] Insufficient enrolment.

Adjunctive therapy studies in patients with partial-onset seizures

In a multicentre, double-blind, parallel-group study (Study AE-ET1), 647 adults with partial seizures receiving concomitant AEDs were randomized to one of four rufinamide treatment groups (200, 400, 800 or 1600 mg/day, administered b.i.d.) or the placebo group [22,29]. There was a 3-month prospective baseline phase, and patients who had nine or more seizures entered a 3-month double-blind phase. There was a statistically significant linear trend of dose response in seizure frequency per 28 days in the treatment group ($P = 0.003$) and in responder rates (patients with ≥50% decrease in seizure frequency compared with baseline) ($P = 0.00319$). A pairwise comparison of median seizure frequency between placebo and each rufinamide arm revealed a significant reduction in seizures in patients treated with rufinamide 400 mg/day (an 11% decrease, $P = 0.00274$), 800 mg/day (16%, $P = 0.00123$) and 1600 mg/day (17%, $P = 0.00163$) compared with placebo.

Study AE-PT2 was a small multicentre, double-blind, parallel-group weekly rising dose study in 50 adult patients who were on one or two concomitant AEDs [30]. In addition to patients with partial seizures, patients with primary generalized tonic–clonic seizures could be enrolled. Subjects were randomized to 400, 800, 1200 or 1600 mg/day groups or to the matching placebo. On day 1 all patients received a single 800-mg dose of rufinamide. On day 7 patients entered a double-blind phase and were started on 400 mg/day or on the matching placebo. Dose was increased on a weekly basis depending on the randomized group of 800, 1200 and 1600 mg/day. Patients on rufinamide had a median seizure frequency ratio during the treatment phase of 0.59 compared with 1.52 for the placebo group. Responder rates analysis did not reveal any statistically significant differences. This study had significant deficiencies, including a small sample size, a retrospective baseline and inclusion of some patients with no seizures at baseline.

In Study 0021A, which also had a double-blind, parallel-group, adjunctive therapy design, adults with refractory partial seizures were randomized to add-on treatment with either 3200 mg of rufinamide ($n = 156$) or placebo ($n = 157$) [31–33]. Patients ≥16 years of age weighing >18 kg who were on a stable dose of one or two AEDs entered a 56-day baseline phase. Those who had at least six partial seizures were randomized to placebo or rufinamide, starting with a dose of 800 mg/day and increasing this by 800 mg every 2 days to a target dose of 3200 mg/day for 7–14 days. They then entered a 77-day maintenance phase. The median percentage change in partial seizure frequency during the treatment phase relative to the baseline phase was statistically significantly in favour of rufinamide (20.4% reduction in the rufinamide group compared with 1.6% increase in the placebo group, $P = 0.0158$). In the rufinamide group, 28.2% of the patients were responders compared with 18.6% in the placebo group ($P = 0.0038$).

Study E2080-301 is an ongoing double-blind parallel-group study in patients (12–80 years of age) with refractory partial seizures who receive one to three AEDs and have at least six seizures during an 8-week baseline. Patients are randomized to add-on therapy with either rufinamide 1600 mg b.i.d. or placebo. Patients entered a 12-day titration phase beginning with 400 mg b.i.d. or placebo. The dose was increased every 3 days to 1600 mg b.i.d. The patients continued in a 12-week maintenance phase. It is estimated that a total of 408 patients will be included.

A paediatric multicentre, double-blind, adjunctive therapy, parallel-group study (Study 0021P) has also been completed [34]. Children with inadequately controlled partial seizures were randomized to receive either placebo or rufinamide, 45 mg/kg. Patients 4–16 years of age who were on a stable dose of one or two AEDs entered a 56-day baseline phase. Patients who experienced six or more partial seizures were redosed to placebo or rufinamide. They entered a 7- to 14-day titration phase. Depending on weight, they were dosed with 10 mg/kg daily for 2 days or 200 mg/day for patients weighing 18–30 kg (group A); 400 mg/day for patiients weighing 30–50 kg (group B); and 600 mg/day for patients weighing 50–60 kg (group C). The dose was increased by 10 mg/kg every 2 days to reach a target dose of 45 mg/kg on days 7–14, not exceeding 1000 mg in group A, 1800 mg/day in group B or 2400 mg/day in group C. The maintenance phase lasted 77 days, and 268 patients received a study drug; 136 were on rufinamide and 132 on placebo. The mean percentage reduction in partial seizure frequency during the 28-day double-blind phase relative to the baseline phase (primary efficacy variable) was 12.8% in the rufinamide group compared with 7% in the placebo group, a difference which was not considered statistically significant ($P = 0.06214$).

Adjunctive therapy in patients with generalized epilepsies

Primary generalized tonic–clonic seizures

In a multicentre, double-blind, parallel-group study (Study 0018), patients 4 years of age or older with inadequately controlled primary generalized tonic–clonic seizures, receiving one or two AEDs, and with at least three generalized tonic–clonic seizures during an 8-week baseline, were randomized to add-on therapy with either rufinamide 800 mg/day ($n = 78$) or placebo ($n = 75$). Patients entered a 56-day baseline phase followed by a 140-day double-blind phase [35]. The mean age of the patients was 29.3 years (range 4–63 years), and the median number of generalized tonic–clonic seizures per 28 days during the baseline period was 3.5 (range 1.5–84) for the rufinamide group and 4 (range 1.5–74) for the placebo group. The median reductions in seizure frequency were 36.4% and 25.6% for the rufinamide and the placebo group, respectively, differences that were not statistically significant ($P = 0.633$). However, the rufinamide dosage used in this study was low compared with all the other placebo-controlled rufinamide studies, which might have contributed to the negative outcome of this study.

Lennox–Gastaut syndrome

The study in Lennox–Gastaut syndrome (Study 0022) also used a multicentre, double-blind parallel-group design [28,36–38]. Patients were randomized to add-on therapy with either placebo ($n = 64$) or rufinamide at a dose of 45 mg/kg ($n = 74$); patients underwent a 28-day baseline phase followed by a 14-day titration phase and then a 70-day maintenance phase. There was a statistical difference between the two treatment groups in all three of the primary efficacy variables, including percentage change in total seizure frequency, percentage change in tonic–atonic seizure

frequency, and seizure severity ratings. Patients in the rufinamide group experienced a 32.7% median reduction in total seizure frequency per 28 days relative to baseline, compared with 11.7% for the placebo group ($P = 0.015$). Patients on rufinamide also had a 42.5% median reduction in tonic–atonic seizure frequency per 28 days relative to the baseline, compared with a 1.4% median increase for the placebo group ($P = 0.0001$). An improvement in seizure severity was observed in 53.4% of patients assigned to rufinamide compared with 30.6% of those assigned to placebo ($P = 0.0041$). Of the patients who completed the study, 124 entered an extension phase for up to 36 months. The median reduction in total seizures after 12 months compared with the pre-double-blind baseline was over 43%, and the median reduction in tonic–atonic seizures, in particular, was over 58%.

General overview of efficacy data in epilepsy

The mixed outcomes of the double-blind efficacy studies may be due to various causes. In the 0018 study of patients with primary generalized tonic–clonic seizures, the active group was randomized to only 800 mg/day, which is significantly lower than the typical dose of 1600–3200 mg/day. Another possible factor is the inclusion of a high number of patients taking enzyme-inducing AEDs, which reduce considerably the plasma rufinamide levels, resulting in a possible impact on efficacy. Other pharmacokinetic factors might relate to the fact that in many early studies a formulation with suboptimal bioavailability was used, and to the possibility that administration at the time of food intake (a condition known to increase rufinamide bioavailability) might not have been sufficiently controlled.

Nevertheless, the modest percentage reduction in seizure frequency in the various studies suggests at least a moderate level of efficacy with this medication.

Studies in other indications

Rufinamide's mechanism of action suggests a potential value in neuropathic pain [39]. To investigate this possibility, a double-blind, randomized, parallel-group study in diabetic neuropathy was conducted. Sixty patients were randomized to rufinamide (2400 mg/day) and 63 to placebo. The primary efficacy variable (total score of the short-form McGill Pain Questionnaire at the end of the double-blind treatment) did not show any statistical difference between the two treatment groups ($P = 0.3552$). Patients in the rufinamide group experienced a 7.9-point decrease in the total pain score relative to baseline compared with a 5.6-point decrease in the placebo group. The visual analogue scale test also did not show any statistically significant difference between the two groups.

Adverse effects

Overall safety profile

As of November 2005, 1978 patients with epilepsy had been treated with rufinamide in studies. Of these, 1240 were exposed during double-blind studies. In addition, 188 healthy volunteers were exposed to rufinamide during phase I studies and 60 patients with neuropathic pain were also exposed during early clinical studies. Table 51.2 summarizes the safety experience from adjunctive therapy double-blind trials in adults with partial seizures by listing percentages of patients in whom adverse events occurred (more than 5% of of those treated with rufinamide) and in whom these events occurred with a higher incidence than in the placebo group (Table 51.3). The average daily dose was 1700 mg/day. In this analysis, which included a total of 720 patients exposed to rufinamide and 290 exposed to placebo, 80.6% of patients had an adverse event in the rufinamide groups compared with 81.4% in the placebo groups. Headache, dizziness, fatigue, nausea and somnolence were the most commonly reported adverse events [1].

Adverse events were typically mild to moderate in severity. The discontinuation rate, owing to adverse events in patients with partial epilepsy, was 10% for the rufinamide groups and 6% for the placebo groups. The most common causes for discontinuation in the rufinamide groups were dizziness, fatigue, headache, diplopia, nausea and ataxia. The rate of any adverse events and the most frequently reported adverse events increased as dosages were increased.

The adverse events that occurred in more than 10% of all treated patients were compared between the rufinamide ($n = 1240$) and the placebo ($n = 635$) groups. Krauss *et al.* [41] received safety data from 23 studies involving patients with epilepsy. Eleven of these were randomized, double-blind, placebo-controlled studies and 12 were open-label studies. The analysed

Table 51.2 Rufinamide dosing schedule.

Study day (Titration phase)	Approximate dose (mg/kg/day)	18.0–29.0 kg	29.0–50.0 kg	50.0–70.0 kg	+70.1 kg
1–2	10	200	400	800	800
2–4	20	400	800	1200	1600
5–6	30	800	1200	1600	2400
7	40	1000	1800	2400	3200

Rufinamide or matching placebo was administered orally with breakfast and again with supper or an evening snack. A lower titration schedule (over 14 days) was allowable at the discretion of the investigator if tolerability issues became apparent.

Table 51.3 Adverse events for adult double-blind partial epilepsy studies occurring in >5% of population in rufinamide versus placebo.

Adverse events	Rufinamide[a] (%)	Placebo[b] (%)
Any adverse event	*80.6*	*81.4*
Headache	27.6	26.2
Fatigue	17.6	11.7
Nausea	11.7	10.0
Somnolence	10.4	7.2
Diplopia	9.9	3.1
Tremor	6.1	4.5
Blurry vision	6.0	3.1
Nystagmus	5.3	4.5

[a] $n = 720$.
[b] $n = 290$.

population comprised children, adolescents and adults with partial-onset epilepsy, generalized epilepsy or Lennox–Gastaut syndrome. Short-term therapy safety data from double-blind studies included data on 1240 patients who received at least one dose of rufinamide and 635 who were on placebo. Sex distribution was similar: 620 males (50%) in the rufinamide group and 338 (53.2%) in the placebo group. The age distribution in the rufinamide group was <12 years of age (9.6%), 12–16 years (7.5%), 17–64 years (82.2%), >65 years (0.7%) and in the placebo group 17.6%, 13.2%, 68.2% and 0.9%, respectively. In the double-blind trials the most common adverse events (rufinamide versus placebo group,) in all age groups were headache (22.9% versus 8.9%), dizziness (15.5% versus 9.4%), fatigue (13.6% versus 9%), somnolence (11.8% versus 9.1%) and nausea (11.4% versus 7.6%). Typically, the rate of an adverse event increased when doses increased. Adverse events leading to study discontinuation occurred in 8.1% of the rufinamide group compared with 4.3% on placebo. A total of 1978 patients participated in open-label long term trials, of whom 50.5% were male. The mean age was 31.3 (1–81) years: 11.8% were <12 years of age, 9.3% 12–16 years of age, 77.6%, 17–64 years of age and 1.4% > 65 years of age. The most common adverse events were headache (29.5%), dizziness (22.5%) and fatigue (17.7%) and most adverse events were mild to moderate in severity. Adverse events leading to discontinuation occurred in 259 patients (13.1%); the most common ones were fatigue (38), headache (32), dizziness (31) and nausea (31). Of the reported adverse events in the rufinamide groups, 31.8% were mild, 36.1% were moderate and 10.7% were severe. In the placebo groups, these percentages were 37.8%, 31.3%, and 9.1%, respectively. The percentage of rufinamide-treated patients experiencing serious adverse events was 6.3% compared with 3.9% of the placebo-treated patients in the double-blind studies. Two deaths were reported in the rufinamide groups and four in the placebo groups. No patients experienced Stevens–Johnson syndrome or toxic epidermal necrolysis. During long-term therapy, common adverse events were similar to those observed during the short-term blinded studies. The majority of these were mild to moderate in severity and they typically occurred during the first 2 weeks of therapy. Rufinamide doses up to 7200 mg/day did not result in any significant symptoms of toxicity.

The safety data in the paediatric patients who participated in double-blind, placebo-controlled studies were also analysed. Of these, 212 received rufinamide and 197 received placebo. The median age was 11 years, the median body weight was 36 kg and the median daily dose of rufinamide was 42.0 mg/kg. The median duration of exposure was 3 months. The most common adverse events (rufinamide versus placebo) were somnolence (17% versus 8.1%), vomiting (16.4% versus 7.1%), headache (16% versus 8.1%) and pyrexia (11.3% versus 10.7%). Discontinuation rates as a result of adverse events were 7.1% for the rufinamide group and 2% for the placebo group.

Effect on cognitive functions

A positive cognitive profile of rufinamide was suggested by experimental studies in rodents indicating improvement in learning performance in the step-down passive avoidance paradigm, and ability to partially counteract electroshock-induced amnesia. Aldenkamp and Apherts [40] conducted neuropsychiatric testing in 189 patients with partial seizures (age range, 15–64 years) who received rufinamide 200, 400, 800 or 1600 mg/day as add-on treatment in a multicentre, double-blind, placebo-controlled parallel-group study [40]. Cognitive testing was done at baseline and after 3 months of treatment. The results did not reveal any statistically significant decline for patients taking any of the doses of rufinamide compared with baseline.

Current place in therapy

Rufinamide has shown significant efficacy in the trial in Lennox–Gastaut syndrome, and it has been approved for this indication in Europe. Approval for this indication in the USA is currently pending. Suggested maintenance dosages in Europe for the treatment of Lennox–Gastaut syndrome are 200–1000 mg/day (200–600 with valproic acid co-medication) for patients weighing less than 30 kg, and 400–1800 mg/day, 400–2400 mg/day and 400–3200 mg/day for patients weighing 30–50 kg, >50–70 kg and >70 kg, respectively [41]. Higher doses have been used in open-label studies in adults, up to 4800 mg/day. The drug should be given in two divided daily doses, taken at meal times.

Concerning other indications, a study in patients with primary generalized tonic–clonic seizures was negative, which might have been in part due to the low rufinamide dose tested (800 mg/day). Efficacy as add-on therapy has been demonstrated in adults with partial epilepsy. One monotherapy study was negative and one short-term monotherapy study was positive. An ongoing add-on study in partial epilepsy is close to completion.

Pending results of further trials and reports from initial post-marketing experience, there are insufficient data to determine the current role of rufinamide in the treatment of epilepsy. At present, the best-defined indication is the adjunctive treatment of patients with Lennox–Gastaut syndrome who did not respond to first-line therapies.

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52 Stiripentol

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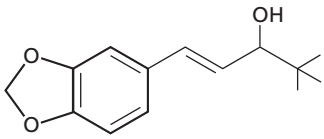

Primary indications	Adjunctive therapy of refractory generalized tonic–clonic seizures associated with severe myoclonic epilepsy in infancy (Dravet's syndrome) in patients receiving valproic acid and clobazam
Usual preparation	Capsules: 250 and 500 mg Sachets (powder for oral suspension): 250 and 500 mg
Usual dosages	50 mg/kg/day, to be reached over 3 days
Dosing frequency	Two or three times per day
Significant drug interactions	Enzyme-inducing antiepileptic drugs increase stiripentol clearance by stimulating its metabolism. Stiripentol inhibits the metabolism and increases the serum concentration of phenobarbital, carbamazepine, phenytoin, primidone, clobazam, *N*-desmethylclobazam and valproic acid
Serum level monitoring	There is insufficient information on the value of monitoring serum stiripentol levels
Reference range	Not clearly defined
Common/important adverse effects	Drowsiness, ataxia, tremor, hypotonia, dystonia, hyperactivity, aggressiveness and other behaviour disorders, insomnia, nausea, anorexia, weight loss, vomiting and haematological abnormalities (e.g. neutropenia and thrombocytopenia)
Main advantages	Robust efficacy in severe myoclonic epilepsy of infancy
Main disadvantages	Drug–drug interactions, complex pharmacokinetics
Mechanism of action	Not fully understood, but probably includes potentiation of GABAergic transmission. Interactions with concomitant medications contribute to efficacy and averse effects
Oral bioavailability	≥70%
Time to peak levels	0.5–2 h
Elimination	Primarily by metabolism, including glucuronide conjugation, opening of the methylenedioxy ring with formation of a dihydroxyderivative, and O-methylation of catechol metabolites
Volume of distribution	Not known
Elimination of half-life	In the order of 4.5–13 h. Stiripentol follows Michaelis–Menten kinetics, and half-life increases with increasing serum concentrations. As a result, steady-state serum concentrations increase more than proportionately after a dose increment
Plasma clearance	Dose-dependent (clearance decreases with increasing dosage). In adults co-medicated with enzyme inducers, apparent oral clearance decreases from 1.7 L/h/kg at 600 mg/day to 0.35 L/h/kg at 2400 mg/day

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Protein binding	99%
Active metabolites	None known
Comment	A potentially valuable drug for difficult-to-treat cases of severe myoclonic epilepsy in infancy

Introduction

Stiripentol is a novel antiepileptic drug (AED) that belongs chemically to the class of aromatic allyl alcohols, and is therefore structurally unrelated to other currently marketed AEDs [1]. Its main mechanism of action in experimental models has been postulated to involve an increase in gamma-aminobutyric acid (GABA)-ergic neurotransmission [2].

Stiripentol has been developed during the last 30 years and used under a special programme in France and Canada for more than 10 years [3,4]. Stiripentol was given orphan drug designation in 2001 in the European Union, and conditional marketing authorization was granted in January 2007 by the European Medicines Agency (EMEA) [5] as the first orphan AED in children, for the treatment of refractory generalized tonic–clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome), adjunctively to valproic acid and clobazam.

In clinical trials, assessment of its potential antiepileptic efficacy has been complicated by pharmacokinetic interactions, which result in marked increases in the serum levels of many concomitantly administered AEDs [1].

Chemistry

Stiripentol (4,4-dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol) belongs to the family of aromatic allyl alcohols. Stiripentol is a chiral molecule with an asymmetric carbon atom at the 3 position [6]. Stiripentol is produced as a racemate, i.e. as a mixture of *R*(+)-stiripentol and *S*(−)-stiripentol in equal proportions.

Stiripentol has a molecular weight of 234. It is virtually insoluble in water and soluble in ethanol and acetone.

Pharmacology

The antiepileptic activity of stiripentol was discovered in the 1970s. The compound shows anticonvulsant effects in the pentylenetetrazole and maximal electroshock models [7,8], as well as in other models [9]. In the pentylenetetrazole model in the rat, *R*(+)-stiripentol is 2.4 times more potent than *S*(−)-stiripentol [10], and it also has a shorter half-life than *S*(−)-stiripentol (2.8 h versus 6.5 h). After repeated administration of the racemate to rats, a five- to sixfold increase in the *S*(−)-stiripentol/*R*(+)-stiripentol ratio was observed compared with the ratio found after a single dose [10]. This phenomenon may explain the observation that after chronic dosing in rats tolerance develops to its protective effects against pentylenetetrazole-induced seizures [8].

The mechanism of action of stiripentol is not fully understood. However, stiripentol has actions on GABA-mediated transmission. In neurochemical studies, stiripentol reduced synaptosomal uptake of GABA and caused a small (+22%) increase in the concentrations of GABA in the brain [7]. Stiripentol has no affinity for either $GABA_A$ or $GABA_B$ receptors [2,7]. Recently, stiripentol has been shown to enhance $GABA_A$ receptor transmission in CA3 pyramidal neurones in the neonatal rat at clinically relevant concentrations (30–200 μmol) [2]. Results from this study suggests that stiripentol may modulate GABAergic function by acting at the barbiturate binding site and thus increasing the duration of opening of the $GABA_A$ receptor-activated chloride channels [2].

Pharmacokinetics

There are only limited published data on the pharmacokinetics of stiripentol in humans. Studies have been carried out in a small number of healthy volunteers and adult patients with epilepsy.

Stiripentol is rapidly absorbed, with peak serum concentrations being observed at 0.5–2 h [6]. The absolute oral bioavailability of stiripentol is not known. Bioequivalence between the capsules and the oral suspension formulations has not been established. Stiripentol should be taken with food because it degrades rapidly in an acidic environment, such as in gastric contents in a fasting state (for further details see ref. 32). It should not be taken with milk, dairy products, carbonated drinks, fruit juices or food and drinks that contain caffeine or theophylline (see ref. 32).

Stiripentol is highly (99%) bound to plasma proteins, and its distribution from the central compartment is slow, making the decline in serum concentration after a single dose multiphasic [11].

Stiripentol has non-linear Michaelis–Menten pharmacokinetics and, as a result, dose increments produce disproportionately larger increments in serum concentration at steady state [11]. Stiripentol clearance also decreases during repeated dosing, presumably inhibiting the enzymes responsible for its metabolism (see ref. 32). In a study conducted in patients with epilepsy who received concomitant enzyme-inducing AEDs, mean apparent oral clearance values were about 1.66 L/kg/h at a dose of 600 mg/day, and 0.83 L/kg/h and 0.35 L/kg/h at daily doses of 1200 mg and 2400 mg, respectively [12]. Because stiripentol clearance is subject to enzyme induction, clearance values in

patients not receiving enzyme inducing co-medication are much lower. The elimination half-life of stiripentol is in the range of 4.5–13 h, increasing with increasing dose (see ref. 32). Non-linearity of stiripentol pharmacokinetics is presumably a result of the saturation of the enzyme systems responsible for the metabolism of the drug [13].

Stiripentol is extensively metabolized in the liver. Altogether five different metabolic pathways have been identified in humans, the most important being glucuronide conjugation, opening of the methylenedioxy ring with formation of a dihydroxy derivative, and O-methylation of catechol metabolites [9]. None of the human metabolites displays pharmacological activity. Over 70% of the dose can be recovered in the urine as 13 different metabolites [14].

There are no published data on the pharmacokinetics of stiripentol in special patient groups, such as pregnant women, elderly subjects or patients with hepatic or renal dysfunction. Also, detailed pharmacokinetic data in children are lacking.

Drug interactions

Stiripentol has a number of clinically significant interactions with other AEDs, mainly as a result of stiripentol's ability to potently inhibit the activity of several cytochrome P450 (CYP) isoenzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 [15]. On the other hand, AEDs with enzyme properties accelerate the elimination of stiripentol. The clearance of stiripentol is increased by 300% by carbamazepine, phenobarbital and phenytoin [12].

Stiripentol dose-dependently inhibits the metabolism of phenytoin. The clearance of phenytoin has been found to be reduced by 38% and 78% at stiripentol doses of 1200 mg/day and 2400 mg/day, respectively [12]. The degree of interaction shows wide interindividual variation, but reductions of phenytoin dose of 25–66% may be necessary. The clearance of carbamazepine is reduced by about 50% using stiripentol [16,17]. The effect of stiripentol on carbamazepine metabolism builds up gradually over 7–10 days [16], and, after starting stiripentol, the dosage of carbamazepine should be reduced in steps by a total of 50% to avoid toxicity. Stiripentol also increases the serum concentrations of phenobarbital, primidone, clobazam and, to a much greater extent, *N*-desmethylclobazam (derived metabolically from clobazam) [18–20]. A reduction of about 30% in the dose of phenobarbital may be necessary [18], and reductions may also be needed in clobazam dosage. The increase in serum clobazam and *N*-desmethylclobazam levels may explain the clinical observation that stiripentol appears to enhance the potency of clobazam [20]. Stiripentol may also inhibit the metabolism of valproic acid, but the effect is modest, and a reduction in valproic acid dose may not be necessary [21].

Serum level monitoring

The relationship between serum stiripentol concentrations and clinical effects has not been adequately investigated, and stiripentol levels are not routinely monitored during stiripentol therapy.

Efficacy

Stiripentol has been developed for the last 30 years [4]. Most of the reported clinical studies have been open-label, uncontrolled add-on trials in adults and children with refractory epilepsies. Maintenance dosages of stiripentol in the published studies have been in the range of 1200–3000 mg/day in adults and 20–90 mg/kg/day in children.

One of the first published studies of stiripentol was carried out in the 1980s with seven patients with complex partial seizures [22] in whom adjunctive therapy with stiripentol resulted in reduction of seizure frequency. Another early study [23] reported that 66% of partial epilepsy patients demonstrated at least 50% seizure reduction, and similar results were obtained in a trial assessing stiripentol in refractory partial epilepsy in patients co-medicated with carbamazepine [24]. In other early uncontrolled studies, stiripentol was reported to decrease the frequency of generalized seizures, including typical and atypical absences [25,26]. Overall, however, these results are difficult to interpret because of their uncontrolled nature and because observed improvements in seizure control might have been produced by an increase in the serum concentrations of concomitant AEDs. Attempts to discontinue stiripentol co-medication have resulted in some studies in worsening of seizure control, which may suggest that stiripentol may have only little independent antiepileptic efficacy. Clinical studies of stiripentol in adults were discontinued in 1995 when no significant efficacy was found in a controlled trial in which stiripentol was combined with carbamazepine [9].

In 2006, Perez *et al.* [27] reported the results of a single-blind, add-on placebo-controlled paediatric trial of 108 patients with refractory epilepsies, combined with a further open trial of 104 other selected patients with epilepsy syndrome. Of the patients included in the placebo-controlled part of the study, 49% showed a 50% reduction in seizure frequency and 10% became seizure free. This study also reported for the first time the efficacy of stiripentol in patients with SMEI; 10 of the 20 children with SMEI responded, all of whom were treated with clobazam as co-medication. Subsequently, these promising results in SMEI were confirmed by a randomized, placebo-controlled, double-blind trial in 41 children [20], 71% of whom showed a more than 50% reduction of seizure frequency after stiripentol (50 mg/kg/day) was added to valproic acid and clobazam. Nine of these 41 children became free of clonic or tonic–clonic seizures, at least during the short evaluation period (second month of treatment) of the trial. Whether the observed benefit was the result of a direct action of stiripentol or was mediated by an increase in the serum levels of co-medication (most notably *N*-desmethylclobazam, the serum concentration of which increased prominently) is unclear.

The role of stiripentol in the treatment of SMEI has most recently been evaluated by Kassai *et al.* [28] in a meta-analysis in which they used a fixed-effect model to summarize the odds ratio of seizure rates and a logistic model to evaluate the influence of patient characteristics on treatment effect in uncontrolled and controlled randomized studies that compared stiripentol with placebo. The odds ratio of response to stiripentol relative to placebo was found to be 32 (CI 6.2–161) and seizure reduction rate was 70% (CI 47–93%). However, in this analysis there were no differences between subgroups and type of con-

comitant AEDs. Results of uncontrolled studies were seen as potentially biased, but the two randomized controlled trials were rated as reliable and showed that seizure frequency was greatly reduced by stiripentol in children with SMEI after 2 months of treatment.

The use of stiripentol in children with focal epilepsy was evaluated again in a randomized placebo-controlled setting with enrichment and withdrawal, designed by Chiron *et al.* [29]. Among the 67 children who entered a 4-month open label stiripentol add-on phase after a 1-month single-blind placebo baseline, 32 responders were randomized for 2 months either to continue stiripentol (n = 17) or to withdraw to placebo (n = 15). The primary endpoint was an increase in seizures over 50% compared with pre-randomization phase, and for this endpoint there was a non-significant difference between stiripentol (n = 6) and placebo (n = 8). A decrease in seizure frequency compared with baseline, which was the secondary endpoint, was greater on stiripentol (75%) than on placebo (22%). Twelve (71%) patients experienced at least one adverse event on stiripentol compared with four (27%) patients on placebo, but none of the adverse events was reported as severe.

Adverse effects

Currently available data indicate that stiripentol is relatively well tolerated. The most commonly reported adverse effects are drowsiness, ataxia, tremor, hypotonia, dystonia, hyperactivity, aggressiveness and other behaviour disorders, insomnia, nausea, anorexia, weight loss, vomiting and haematological abnormalities, for example neutropenia and thrombocytopenia [1,30]. Some adverse effects can be attributed to increased serum levels of concomitant AEDs following administration of stiripentol.

In the double-blind trial in SMEI [20], drowsiness, hyperactivity and aggressiveness were reported in 91% of patients on stiripentol and in 25% of those on placebo. Gastrointestinal adverse effects were also prevalent, 67% in the stiripentol group compared with 35% in the placebo group. None of the patients withdrew from the study because of these adverse effects. Even though the overall incidence of adverse effects is relatively high, many of these may result from increased serum levels of concomitant AEDs and can be managed by adjusting the doses of the latter. The impact of stiripentol on psychomotor development, a major concern in SMEI patients, is unknown [1].

Current place in therapy

Results of add-on studies of stiripentol in adults with focal epilepsy have been disappointing, but controlled add-on trials in paediatric populations suggest that stiripentol is efficacious in SMEI, a severe form of early childhood epilepsy and one of the most intractable epilepsy syndromes in childhood. No other AED has presented similar efficacy in SMEI, and a follow-up report from France [31] demonstrated the long-term efficacy also of stiripentol when added on to valproic acid and benzodiazepines in these patients. Even though these results necessitate further research on larger populations, stiripentol was granted orphan drug status and a conditional marketing authorization in the European Union in January 2007 for the treatment of refractory generalized tonic–clonic seizures associated with SMEI adjunctively to clobazam and valproic acid [32].

Overall, available data indicate that stiripentol can be very valuable as adjunctive therapy in the management of SMEI patients who have not responded favourably to the combination of clobazam and valproic acid. The recommended mean dose in children is 50 mg/kg/day, divided into two or three doses taken during a meal. Treatment is usually started with a lower dose, and is gradually increased to the recommended dose over 3 days. The interactions of stiripentol with many AEDs as a result of the inhibition of several CYP isoenzymes, including CYP3A4, create a need to adjust the doses of the concomitant drugs to improve the tolerability of the treatment. Even although stiripentol has definite CNS and gastrointestinal adverse effects, it seems to be, overall, relatively well tolerated.

Future studies with stiripentol should be aimed at characterizing its bioavailability, pharmacokinetic profiles in children, efficacy when combined with the maximum safe doses of clobazam and valproic acid (to determine whether stiripentol has any independent effect, in addition to increasing serum levels of comedications, particularly *N*-desmethylclobazam), effects on psychomotor development (particularly after early use in the course of the disorder), long-term efficacy and possible long-term adverse effects on growth rate.

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53 Tiagabine

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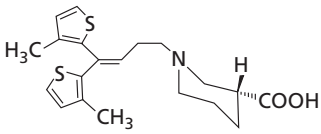

Primary indications	Adjunctive therapy of partial seizures, with and without secondary generalization
Usual preparation	Tablets: 2.5, 5, 10 and 15 mg, expressed as free base (in the USA, Canada and Mexico, strengths are 2, 4, 12, 16 and 20 mg, expressed as tiagabine hydrochloride)
Usual dosages	Starting dosage: 4 or 5 mg/day, which may be increased by weekly increments of 4 or 5 mg/day Maintenance: 15–32 mg/day (30–56 mg/day for patients co-medicated with enzyme-inducing drugs)
Dosing frequency	Two to four times per day
Significant drug interactions	Enzyme-inducing antiepileptic drugs increase tiagabine clearance by stimulating its metabolism
Serum level monitoring	Monitoring serum tiagabine levels is not generally regarded as useful in individualizing tiagabine therapy
Reference range	0.02–0.2 mg/L (this reference range corresponds to tiagabine concentrations most frequently recorded in patients receiving therapeutic doses)
Common/important adverse effects	Dizziness, asthenia, nervousness, tremor, attention/concentration difficulties, depressed mood, language problems, seizure exacerbation (myoclonic and absence seizures, non-convulsive status epilepticus)
Main advantages	Mechanism of action distinct from that of other antiepileptic drugs, and clearly demonstrated efficacy in partial seizures
Main disadvantages	Short half-life necessitating multiple daily dosing, need for slow dose titration, CNS adverse effects and efficacy spectrum restricted to partial seizures
Mechanism of action	Inhibition of GABA reuptake
Oral bioavailability	Close to 100%
Time to peak levels	0.5–2.3 h
Elimination	Primarily by oxidative metabolism mediated by cytochrome CYP3A4
Volume of distribution	About 1.2 L/kg
Elimination of half-life	5–9 h (2–4 h in patients receiving enzyme-inducing co-medication)
Plasma clearance	About 2–3 mL/min/kg (about 4–6 mL/min/kg in patients receiving enzyme-inducing drugs). Children show higher clearance values
Protein binding	96%
Active metabolites	None
Comment	A valuable drug for the adjunctive treatment of refractory partial seizures

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Introduction

Tiagabine is a γ-aminobutyric acid (GABA) uptake inhibitor that was developed in the early 1990s as part of a strategic programme aimed at identifying orally active GABA uptake inhibitors with improved ability to cross the blood–brain barrier compared with nipecotic acid. Tiagabine has proven effective as add-on therapy in patients with refractory partial seizures with or without secondary generalization.

Chemistry

Tiagabine corresponds chemically to (–)-*(R)*–1-[4,4-bis(3-methyl–2-thienyl)-3-butenyl]-3-nipecotic acid hydrochloride. It has an empirical formula of $C_{20}H_{25}NO_2S_2HCl$ and a molecular weight of 412.0. Tiagabine is soluble in water and virtually insoluble in *n*-heptane.

Pharmacology

Activity in animal models of seizures and epilepsy

The anticonvulsant actions of tiagabine have been studied against seizures induced by electrical, chemical and sensory stimuli, and in genetic models of epilepsy. Tiagabine given intraperitoneally (i.p.) was shown to protect against audiogenic seizures in mice, tonic or clonic seizures induced by methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate and pentylenetetrazole in mice and by pentylenetetrazole in rats [1]. However, tiagabine did not protect against maximal electroshock-induced tonic seizures in mice or rats [2,1], and did not prevent tonic or clonic seizures induced by the potassium channel antagonists dendrotoxin or 4-aminopyridine in mice [3,4].

When administered intraperitoneally to amygdala-kindled rats, tiagabine attenuates the expression of secondarily generalized seizures, and completely blocks the expression of partial seizures [2]. Tiagabine also suppresses amygdala kindling-induced epileptogenesis in a dose-dependent manner in rats [5].

As with GABA agonists, tiagabine may enhance the occurrence of spike–wave discharges in animal models of non-convulsive generalized epilepsy. In WAG/Rij rats, a genetic model of generalized non-convulsive absence epilepsy, spike–wave discharges were increased by tiagabine 3 and 10 mg/kg i.p., but not by a 1 mg/kg dose [6]. Exacerbation of absence seizures has also been found in rats with genetic absence epilepsy (GAERS; Genetic Absence Epileptic Rat of Strasbourg) and in the lethargic mouse model [7,8].

Walton *et al*. [9] reported that tiagabine was effective in treating status epilepticus in cobalt-lesioned rats. At doses of ≥5 mg/kg i.p., however, tiagabine was also associated with rhythmic high-voltage discharges. At even higher doses, a similar pattern could be produced in normal rats as well.

Tiagabine reduced both seizure-induced damage to pyramidal cells in the hippocampus and impairment of spatial memory associated with hippocampal damage in the perforant pathway stimulation model of status epilepticus in the rat [10]. Neuronal cell death was also reduced by tiagabine in the hippocampus of gerbils subjected to cerebral ischaemia [11] and in the rat cerebral ischaemia model of delayed pyramidal cell death [12].

Mechanism of action

Potentiation of GABAergic inhibition is regarded as one important mechanism of action for some novel antiepileptic drugs (AEDs). GABA uptake inhibitors represent a unique class of AEDs, of which tiagabine was the first to be introduced into clinical practice. This action is thought to offer two potential advantages over direct $GABA_A$ receptor agonists [13]. First, unlike direct agonists, which produce a continuous or non-physiological pattern of receptor stimulation, the inhibition of GABA uptake enhances the effect only of endogenously released GABA, thus retaining physiological specificity. Second, the extent of enhancement of $GABA_A$ receptor-mediated function by a GABA uptake inhibitor will be limited by the amount of GABA released, which is under constant physiological control, thus potentially limiting the side-effect liability of such an inhibitor.

Tiagabine prevents GABA uptake by inhibiting selectively the GAT-1 GABA transporter, with little or no activity on GAT-2, GAT-3 or BGT-1, which also contribute to the uptake of the neurotransmitter into neurones and glial cells after synaptic release [13,14]. Tiagabine's affinity for inhibiting glial GABA uptake is 2.5-fold greater than that for neuronal uptake [15]. Tiagabine is not a substrate for the GABA uptake carrier and is therefore unlikely to act as a false transmitter at GABAergic neurones [3]. Blockade of GABA uptake temporarily prolongs the presence of endogenously released GABA in the synapse [13]. This is the only known mechanism of tiagabine action.

Although both tiagabine and vigabatrin act by enhancing GABA neurotransmission in the CNS, preclinical data show that vigabatrin and tiagabine have different pharmacological profiles and different mechanisms of action at the cellular level [16]. Tiagabine prolongs the duration, but not the magnitude, of the peak inhibitory postsynaptic current, consistent with temporarily sustained levels of endogenously released GABA in the synapse [17]. By contrast, vigabatrin inhibits presynaptic GABA degradation by selective, enzyme-activated irreversible blockade of GABA transaminase, and thus induces a persistent fivefold increase in whole brain GABA concentration, and also high concentrations of GABA in the retina. [18]. Tiagabine does not induce the widespread increase in total brain GABA concentrations that accompanies $GABA_T$ inhibition. Moreover, vigabatrin seems to accumulate in the retina, whereas tiagabine does not [18].

Pharmacokinetics

Key pharmacokinetic features

Tiagabine pharmacokinetics is linear at doses up to 80 mg/day [19]. The drug is rapidly and nearly completely absorbed after oral administration, with peak serum concentrations being attained within 30–90 min of dosing [20,21]. Food delays the time to peak concentration from a mean of 0.9 h to a mean of 2.6 h but does not change the total amount absorbed. Because tiagabine has a short elimination half-life, the smoother absorption produced by concomitant intake of food helps to reduce excessive fluctuations in plasma drug levels during the dosing

interval, and for this reason it is recommended that the drug be taken at meal times, preferably at the end of the meal.

Protein binding is high at 96%, but tiagabine does not displace highly protein-bound drugs, such as phenytoin and valproic acid, from their binding sites. The volume of distribution is approximately 1.2 L/kg [20,21].

The half-life of tiagabine in patients not taking enzyme inducing AEDs is in the order of 5–9 h [19], but much shorter values (2–4 h) are recorded in patients co-medicated with enzyme inducers. Tiagabine is eliminated virtually entirely by oxidative metabolism, mainly by the cytochrome P450 isoform CYP3A4. Less than 1% is excreted unchanged in the urine, and no active metabolites have been identified [22].

Pharmacokinetics in special populations

Pharmacokinetics in relation to age

The apparent oral clearance of tiagabine after multiple dosing in eight elderly subjects was found to be about 30% lower than in younger adults [23]. Elderly patients taking enzyme-inducing co-medication also had tiagabine clearance values that were twice as high as those of age-matched subjects not taking enzyme inducers, indicating that responsiveness to enzyme induction is not impaired in old age [23].

The pharmacokinetics of tiagabine has not been extensively investigated in patients below the age of 12 years. In one study, the apparent oral clearance of tiagabine normalized to body weight was on average markedly higher (by 35–120%, depending on type of co-medication) in 25 children aged 3–10 years than values recorded in historical adult control subjects [24]. This implies that children require higher doses than adults to achieve similar serum drug concentrations. The difference in apparent oral clearance between children and adults was much less when clearance values were normalized for body surface area than for body weight. Children receiving enzyme-inducing co-medication also had higher tiagabine clearance values than children on non-inducing co-medication. In a paediatric study, however, the maximal tolerated doses for children over 2 years old on inducing AEDs were only slightly higher than in children on non-inducing AEDs, and the difference was not significant (0.73 ± 0.44 mg/kg versus 0.61 ± 0.32 mg/kg) [25].

Pharmacokinetics in disease states

The pharmacokinetics of tiagabine is unaffected in patients with renal impairment or in subjects with renal failure requiring haemodialysis [26]. Patients with mild or moderate liver function impairment have been shown to have higher and more prolonged plasma concentrations of both serum total and unbound tiagabine than normal subjects. Patients with hepatic impairment also had more neurological adverse effects. Tiagabine should therefore be given with caution to patients with epilepsy who have a mild to moderate impairment of hepatic function. These patients are likely to require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals compared with patients with normal hepatic function. Patients with mild to moderate impairment of hepatic function should also be monitored closely because of the potential for increased incidence of adverse effects [27]. Tiagabine should not be used in patients with severely impaired liver function.

Drug interactions

There is no evidence that tiagabine causes either induction or inhibition of cytochrome P450 enzymes [20]. Available evidence indicates that tiagabine does not modify the serum concentrations of concomitantly administered drugs [28,21].

Conversely, enzyme-inducing AEDs such as carbamazepine, phenytoin, phenobarbital or primidone increase the hepatic clearance of tiagabine [29], resulting in reduced serum tiagabine levels and a shortening of the half-life to about 2–4 h. *In vitro*, valproic acid may displace tiagabine from plasma protein binding sites, but it is unclear whether serum unbound tiagabine concentrations are increased in patients co-medicated with valproate.

Serum level monitoring

Tiagabine should be titrated according to clinical effect. It is generally not helpful to monitor the serum levels of tiagabine, partly because its short half-life results in considerable fluctuations in serum drug levels during a dosing interval, which makes it difficult to interpret concentration values taken at a single time point. Moreover, due to the high plasma protein binding of tiagabine, total serum concentrations may not provide a reliable estimate of the amount of unbound, pharmacologically active drug. The use of therapeutic drug monitoring for tiagabine is also complicated by the fact that serum tiagabine concentrations are in the nanomolar range, and technically difficult to measure reliably. Based on the above considerations, it is not surprising that clinical effects such as adverse effects have been found to correlate more strongly with dose than with the serum concentration of the drug [30].

Despite these limitations, a tentative reference serum concentration range of 0.02–0.2 mg/L has been suggested, which corresponds to the levels usually encountered in patients taking therapeutic doses [31]. In practice, however, there are no clear indications for monitoring serum tiagabine levels, except for a check for compliance.

Efficacy

Randomized trials in adults with partial epilepsy

Tiagabine has proven effective as add-on therapy in patients with refractory partial seizures with or without secondary generalization. The primary evidence for this is based on five controlled add-on trials in adults with epilepsy unsatisfactorily controlled with other AEDs (Table 53.1).

Cross-over placebo-controlled adjunctive therapy trials

The initial phase II studies of tiagabine in partial epilepsy were two small placebo-controlled, adjunctive therapy, cross-over enrichment trials. In the first of these trials, 94 patients with complex partial seizures, with or without secondary generalization, were started on a tiagabine dose of 8 mg/day, which was gradually increased over a period of up to 8 weeks until seizures

Table 53.1 Data from five double-blind placebo-controlled trials [29–33] and from an integrated analysis [37] of these studies showing the efficacy of tiagabine as add-on therapy in partial epilepsy.

Reference	Number of patients	Daily dose of tiagabine (mg/day)	Responder rate (>50% seizure reduction) for all partial seizures (%)	Placebo (%)
Richens *et al*. [32]	42	33	52	24**
Crawford *et al*. [33]	36	46	40	14*
Uthman *et al*. [36]	297	16	10	4
		32	20	4**
		56	31	4***
Sachdeo *et al*. [34]	318	32 (16 mg b.i.d.)	28	8***
		32 (8 mg q.i.d.)	23	8**
Kälviäinen *et al*. [35]	154	30	10	5
Ben-Menachem [40]	951	16–56	23	9

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

were sufficiently reduced or unacceptable adverse effects occurred [32]. The maximal dose allowed was 52 mg/day. Patients then entered a 4-week fixed-dose, open-label period on the dose attained after titration. Patients were eligible to enter the double-blind cross-over phase if their seizure frequency had been reduced by at least 25% during the fixed-dose period. Eligible patients were randomized under double-blind conditions to switch to placebo or to continue on their previously individualized dose of tiagabine for a 7-week period. After a 3-week washout period, each patient was switched to the alternative treatment, i.e. those who had received tiagabine in the first period were switched to placebo and those who received placebo were switched to tiagabine. The median daily dose of tiagabine in the double-blind phase was 32 mg/day. From the 42 patients who contributed data for both periods of the cross-over phase, responder rates (percentage of patients with at least 50% seizure reduction during the tiagabine period compared with the placebo period) were 26% for complex partial seizures ($n = 42$) and 63% for secondarily generalized tonic–clonic seizures ($n = 27$). The median seizure rate during the tiagabine treatment period was significantly lower than during the placebo period for complex partial seizures ($P = 0.05$) and secondarily generalized tonic–clonic seizures ($P = 0.009$).

The second phase II trial used the same design but allowed a maximal dose of 64 mg/day [33]. The intent-to-treat group comprised 36 patients who received a mean total daily dose of 46 mg in the tiagabine treatment periods. Tiagabine was significantly better than placebo in reducing all partial seizures ($P = 0.002$), complex partial seizures ($P < 0.001$) and partial seizures with secondary generalization ($P = 0.030$). A total of 46% of patients with complex partial seizures had at least a 50% reduction in weekly seizure rates.

Parallel-group placebo-controlled adjunctive therapy trials

In total, 769 patients took part in three randomized multicentre, parallel-group, double-blind add-on studies in which tiagabine was compared with placebo in patients with refractory partial seizures. These studies included a dose–response trial, a dose–frequency trial [twice daily (b.i.d.) versus four times daily (q.i.d.)] and a three times daily dosing (t.i.d.) trial [34–36].

The dose-ranging multicentre study was conducted in the USA in a total of 297 patients with complex partial seizures [36].

Table 53.2 Significantly higher (versus placebo) treatment-emergent CNS-related adverse events reported by ≥1% of tiagabine-treated patients during the experiment period in the three placebo-controlled parallel group add-on epilepsy studies.

Adverse event	Placebo ($n = 275$), *n* (%)	Tiagabine ($n = 494$), *n* (%)
Dizziness	41 (15)	131 (27)**
Asthenia	39 (14)	99 (20)*
Nervousness	8 (3)	50 (10)**
Tremor	9 (3)	46 (9)*
Difficulty with concentration/attention	6 (2)	30 (6)*
Depression	2 (<1)	17 (3)*
Language problems	0 (0)	8 (2)*

From ref. 38 with permission.
* $P < 0.05$; ** $P < 0.01$.

During a 4-week period, patients assigned to tiagabine were given increasing doses until the dose level to which they had been randomized was reached (16, 32, or 56 mg/day, divided in four equal doses). The patients then remained on a fixed dose for 12 weeks of double-blind treatment. Median decreases in 4-week complex partial seizure frequency for the 32-mg (–2.2) and 56-mg (–2.8) tiagabine groups were significantly greater than for the placebo group (–0.7) ($P = 0.03$ and $P < 0.03$, respectively). Overall, 20% and 29% of patients in the 32-mg and 56-mg groups had a 50% or greater reduction in the frequency of complex partial seizures, compared with 4% in the placebo group ($P = 0.002$ and $P < 0.001$, respectively).

The dose–frequency study was conducted in 318 patients in the USA; it lasted for 24 weeks and consisted of an 8-week baseline, a 12-week double-blind treatment phase and a 4-week termination period [34]. During the first month of treatment, doses were increased weekly to 32 mg/day. The treatment groups were placebo, 16 mg tiagabine twice daily and 8 mg tiagabine q.i.d. The median changes in 4-week complex partial seizure rates were –1.6 ($P = 0.055$) for the 16 mg b.i.d. group and –1.2 ($P < 0.05$) for the 8 mg q.i.d. group, versus –0.2 for placebo. Statistically significant differences between the placebo and two tiagabine groups occurred in the proportion of patients experiencing >50% rate reduction for complex partial, simple partial and all partial seizure rates (Table 53.1).

The t.i.d. dosing study was a northern European trial that compared 30 mg/day tiagabine with placebo in 154 patients [35]. The study included a 12-week baseline, an 18-week double-blind treatment phase and a 4-week termination period. The median change from baseline in 4-week complex partial seizure rates was –1.3 for patients on tiagabine, while placebo patients had a median increase of 0.1 in complex partial seizure rates ($P < 0.05$). Tiagabine was significantly more effective than placebo in patients with simple partial seizures with respect to the proportion of patients achieving a seizure reduction of at least 50% (21% versus 6%; $P < 0.05$), but responder rates for all partial seizures did not differ significantly between groups (Table 53.2).

A meta-analysis of these trials showed that the odds ratio of achieving at least 50% seizure reduction was 3.03 (95% CI 2.01–4.58) in favour of tiagabine [37]. The summary odds ratios for each dose indicated increasing efficacy with increasing doses; there was no suggestion that the effect of the drug had reached a plateau at the doses examined in these studies. A 16 mg/day dose has an odds ratio of 2.40 (95% CI 0.65–8.87), which increased to 3.17 (95% CI 2.03–4.96) at doses of 30 or 32 mg/day and 7.95 (95% CI 3.09–20.49) at a dose of 56 mg/day.

Other randomized adjunctive therapy trials

A multicentre, open-label, randomized, parallel-group study compared the efficacy and tolerability of t.i.d. and b.i.d. dosing of tiagabine as adjunctive therapy in refractory partial seizures [38]. A total of 347 patients were randomized and treated (175 t.i.d and 172 b.i.d.). Tiagabine dose was increased stepwise during a 12-week fixed-schedule titration period to a target dose of 40 mg/day. Patients were then followed for a further 12-week flexible-dose continuation phase. A significantly smaller proportion of patients in the b.i.d. group completed the fixed-schedule titration period (73.1% versus 81.4%; OR 0.571; 95% CI 0.331–0.970; $P = 0.038$). The proportion of responders (patients showing at least a 50% decrease in all seizure frequency from baseline) was similar for both groups (44% for b.i.d. dosing and 48% for t.i.d. dosing) during the last 8 weeks of treatment. Seven (4%) patients in the b.i.d. group were seizure free, compared with 14 (8%) patients in the t.i.d. group.

Another multicentre trial was performed to determine whether a combination of AEDs with different mechanisms of action is superior to a combination of AEDs acting with a similar mechanism. In this study, patients on carbamazepine or phenytoin monotherapy with inadequately controlled complex partial seizures were randomized to add-on therapy with tiagabine or phenytoin (if previously receiving carbamazepine) or tiagabine or carbamazepine (if previously receiving phenytoin), and were titrated to an optimal dose under double-blind conditions [39]. Tiagabine ($n = 170$) showed similar efficacy to carbamazepine or phenytoin ($n = 175$) as adjunctive therapy for complex partial seizures, at low average doses of 24–28 mg/day. The study also suggested that tiagabine may be better tolerated when added to phenytoin or carbamazepine than when carbamazepine and phenytoin are added to each other.

Other studies in (predominantly) adult patients with partial epilepsy

In six long-term open-label trials, more than half of 2248 patients were treated with add-on tiagabine for more than 1 year. For each type of partial seizures, 30–40% of the patients obtained considerable improvement, which was maintained after 12 months of treatment [40]. Daily dosages in long-term studies were between 24 and 60 mg in the majority of patients, and mean and median doses were 45 mg/day for most studies. However, up to 15% of patients received a dose between 80 and 120 mg/day after their first year of treatment [30].

Open-label pragmatic studies allow a longer follow-up than trials required for drug registration and more closely mimic routine clinical practice. Three such studies in patients with refractory partial epilepsy have been conducted in Germany, Poland and Spain [41–43]. All of these studies have a longer follow-up period than the pivotal studies, and together included considerably more patients than the studies submitted in the registration dossier. These trials used the more recently recommended slower titration schedule in a total of 1151 patients, aged 3–93 years, who were followed for up to 6 months. Tiagabine was given three times daily, at an initial dose of 5 mg/day with dose increases of 5 mg per week. The maintenance dose was titrated individually according to the product's labelling. The average dose was 30 mg/day (range 5–90 mg). The proportion of patients with at least 50% improvement in seizure frequency varied from 41% to 61%, and 8–22% of patients became seizure free.

Studies in children

Tiagabine has been studied as adjunctive therapy in over 200 paediatric patients. A 4-month, single-blind study carried out at two centres in Denmark and one centre in France evaluated the response to ascending doses (0.25–1.5 mg/kg/day) of tiagabine as add-on therapy in 52 children over 2 years of age with different refractory epilepsy syndromes [25]. Tiagabine appeared to reduce seizures more in localization-related epilepsies than in generalized epilepsies. Seventeen of the 23 patients with localization-related epilepsies entered the fourth dosing period and had a median reduction in seizure rate in the fourth month of treatment of 33% compared with baseline. In comparison, 13 out of 22 children with seven different generalized epilepsy syndromes entered the fourth dosing period, with a median change in seizure rate of 0%. Among generalized seizures, tonic seizures and atypical absences improved to the greatest extent, with median percentage reductions in weekly seizure rate of 77% and 63%, respectively. The overall maximum daily dose of tiagabine received and tolerated (mean ± SD) was 0.65 ± 0.37 mg/kg.

In the USA, use of tiagabine in children with partial epilepsy has been studied as adjunctive therapy in a placebo-controlled, double-blind multicentre study. Altogether 103 children were randomized to placebo and 108 children to tiagabine. The age range varied between 2 and 11 years. The 7-week titration period was followed by a 12-week fixed-dose period. The initial dose of tiagabine was 0.1 mg/kg/day (given in three divided administrations), which was increased weekly by 0.1 mg/kg/day, and the maximum doses were 0.4 mg/kg/day (subjects taking inducers of CYP3A4) and 0.7 mg/kg/day (subjects not taking inducers of CYP3A4). The median seizure reduction was 16% in the placebo group and 25% in the tiagabine group. Altogether, 31% of children in the tiagabine group had a 50% or greater reduction in

seizure frequency compared with 19% in the placebo group (P = 0.021) [44]. The long-term use of tiagabine was studied in an open-label extension study in 152 children [45]. Of the 140 evaluable patients from the long-term follow-up, 10 were seizure free with tiagabine add-on therapy and 13 achieved seizure freedom with tiagabine monotherapy for periods ranging from 9 to 109 weeks. The shortest seizure-free or monotherapy durations were in patients with recent enrolment dates at the time of the report. The dose range was from 4 to 66 mg/day, and the average dose was 23.5 mg/day.

In a preliminary open-label trial in infantile spasms, 6 out of 12 infants had at least a 50% seizure reduction at dosages of 0.5–3.1 mg/kg/day [46].

Efficacy as monotherapy

The efficacy of tiagabine monotherapy was first assessed in a double-blind parallel-group 29-week study, which compared 6 mg/day with 36 mg/day tiagabine in 198 patients with refractory partial epilepsy who underwent gradual withdrawal of pre-existing AEDs after being started on add-on tiagabine [47]. According to the study design, patients were required to exit the trial when predefined criteria for seizure deterioration were met. Altogether, 33% of the patients on the low dose completed the assessment period, compared with 47% of those taking the higher dose. In both dose groups the median frequency of complex partial seizures decreased significantly during treatment compared with baseline ($P < 0.05$). However, a higher proportion of patients in the 36 mg/day group experienced a reduction in complex partial seizures of at least 50% compared with the 6 mg/day group (31% versus 18%, $P < 0.05$).

The second double-blind study was a randomized comparison of slow versus fast switch to tiagabine monotherapy in 40 patients with partial epilepsy uncontrolled by monotherapy with another AED, followed by an open-label evaluation [48]. If the patients did not tolerate the double-blind tiagabine titration scheme, an even slower open-label titration could be used. Thirty-four (85%) of the 40 patients were successfully switched to tiagabine monotherapy in either the double-blind or open-label drug-switching schemes. The results of this trial suggest that up-titration starting at 5 mg/day with weekly increments of 5 mg/day should be recommended in clinical practice. The retention rate in the study for 12 weeks on tiagabine monotherapy was 63% (25/40) and 48% (19/40) for 48 weeks. The initial target dose for tiagabine monotherapy was 10 mg b.i.d., but in the open-label phase tiagabine dose could be adjusted up or down according to the clinical judgement of the investigator up to a maximum daily dose of 70 mg. The median dose was 20 mg/day, with a range from 7.5 to 42.5 mg/day during the first 48 weeks.

A third monotherapy trial compared the efficacy of tiagabine and carbamazepine according to a double-blind, randomized parallel-group design in 290 patients with newly diagnosed partial epilepsy [49]. In the initial 6-week titration period, patients were titrated from tiagabine 5 mg/day or carbamazepine 200 mg/day to tiagabine 10 or 15 mg/day or carbamazepine 400 or 600 mg/day in a stepwise fashion. During the 44-week assessment period the dose could be adjusted within the ranges of 10–20 mg/day for tiagabine and 400–800 mg/day for carbamazepine. Both treatments were administered b.i.d. The study, which has only been published in abstract form, showed a significant difference between the study groups with regard to 'time to meeting an exit criterion' ($P < 0.05$). An exit criterion was either status epilepticus or the occurrence of a second seizure at the maximum tolerated or maximum allowed dose level. The proportion of patients who completed the assessment period either seizure free or with a single seizure was 41% (77 out of 144) in the tiagabine group and 53% (77 out of 144) in the carbamazepine group ($P < 0.05$). It has been suggested that the inferior efficacy of tiagabine compared with carbamazepine in this trial might have been due to the relatively low maximum dose of tiagabine that was allowed.

Adverse effects

Most common central nervous system adverse effects

In placebo-controlled short-term trials, some adverse CNS effects were found to be particularly common in tiagabine-treated patients (Table 53.2). Of these, the most frequent was dizziness, which consists of a feeling of light-headedness or unsteadiness, develops usually within 1–2 h of taking a tiagabine dose and is usually associated with the peak plasma concentration of the drug. Other adverse effects encountered more commonly with tiagabine than with placebo included asthenia (lack of energy), nervousness, tremor, concentration difficulties, depressed mood and language problems (difficulty in finding words or initiation of speech). The increased risk of CNS-related adverse events compared with placebo was evident in the titration period only, and there was no difference in rate of emergence of adverse effects during the fixed-dose period [30]. Altogether, 5% of the placebo patients and 13% of tiagabine patients discontinued prematurely because of adverse events ($P < 0.001$). Again, the majority of tiagabine-treated patients discontinued during titration and discontinuation rates for placebo and tiagabine were similar during the fixed-dose period. This suggests that tiagabine should be titrated slowly.

Central nervous system-related adverse effects were also shown to be clearly dose related in the US monotherapy study, in which a low dose (6 mg/day) and a high dose (36 mg/day) were compared [47]. When the tolerability of t.i.d. and b.i.d. dosing of tiagabine as adjunctive therapy in refractory partial seizures was evaluated [38], the incidence of adverse effects was similar between treatment groups but adverse effects seemed to be more severe in the b.i.d. dosing group, and more patients in the t.i.d. group could complete the study.

Based on these studies, it is recommended that to minimize adverse effects tiagabine should be given initially twice a day, with a change to three times daily dosing when dosages above 30 mg/day are used. Tiagabine should always be taken with food to avoid rapid increases in plasma concentrations. In individual patients, four times daily dosing may be helpful, at least at higher doses. Somnolence and drowsiness were not seen more frequently in tiagabine patients than in patients receiving placebo.

Other central nervous system adverse effects

Psychiatric adverse effects

There has been concern that tiagabine may be associated with an increased incidence of psychosis, particularly with rapid titration. Evaluation of psychosis-related adverse events showed there was no excess risk of this disorder attributable to tiagabine beyond what would be expected in a population with difficult-to-control partial seizures. In the three parallel-group add-on trials, the incidence of psychosis was 0.8% in the tiagabine-treated patients and 0.4% in the placebo-treated patients [30]. However, in clinical trials the proportion of patients with depression was significantly higher in those receiving adjunctive therapy with tiagabine than in those receiving placebo (5% versus 2%) [30]. Because of this concern, if there is a history of behavioural problems or depression, treatment with tiagabine should be initiated at a low initial dose under close supervision, as there may be an increased risk of recurrence of these symptoms during treatment with tiagabine.

Seizure aggravation and status epilepticus

Several cases of non-convulsive status epilepticus have been reported, with disappearance of status after withdrawal of tiagabine or reduction in dosage. In double-blind placebo-controlled trials in patients with partial epilepsy, however, the incidence of spike–wave status or any kind of status epilepticus was 3% (8 out of 275 patients) on placebo and 4% (22 out of 494 patients) on tiagabine, the difference being not statistically significant [50]. Further study of individual cases suggested that most of the subjects with apparently tiagabine-associated non-convulsive status had pre-existing spike–wave patterns and that, in some cases, the condition was related to drug-induced encephalopathy rather than status epilepticus. However, it would be wise not to use tiagabine in patients with unclassified epilepsy or patients with generalized epilepsy, especially those with a history of absence or myoclonic seizures and/or a history of spike–wave discharges on the electroencephalogram (EEG) or non-convulsive status epilepticus [51]. Tiagabine has not been shown to be effective in these patients, and there is evidence that AEDs increasing GABAergic transmission may exacerbate or induce absences or myoclonus [52]. In patients with a history of spike–wave discharges, cognitive or neuropsychiatric disturbances can be associated with exacerbation of the EEG abnormalities. However, in the documented cases of spike–wave discharges on EEG with cognitive/neuropsychiatric events, some patients with partial epilepsies have been able to continue tiagabine but required dosage adjustment [30].

In 2005 the Food and Drug Administration (FDA) announced that a bolded warning was to be added to the US labelling for tiagabine to warn prescribers about the risk of seizures in patients without epilepsy being treated with this drug. The FDA had become aware of reports of the occurrence of seizures in more than 30 patients prescribed tiagabine for conditions other than epilepsy [53]. Most of these uses were in patients with psychiatric illnesses. In addition to the occurrence of isolated seizures, the FDA received several reports of status epilepticus in patients without epilepsy. The use of tiagabine in psychiatric disorders, sleep disorders and drug dependence has been studied in several trials, but the safety and efficacy of tiagabine have not yet been established for indications other than epilepsy and therefore its off-label use should be discouraged [53].

Effects on cognition

The neuropsychological effects of tiagabine given as add-on therapy and as monotherapy have been evaluated, and no adverse effects on cognitive abilities have been demonstrated. In the largest short-term double-blind add-on study, 162 adults completed a multicentre dose–response study with random assignment to placebo or 16, 32 or 56 mg/day tiagabine [54]. The results of 19 measures of cognitive abilities and 18 measures of adjustment and mood showed only findings attributable to chance. Long-term cognitive results have been assessed in a double-blind, placebo-controlled parallel-group add-on study with an open-label extension involving 18- to 24-month follow-up [55]. The neuropsychological and EEG evaluation did not indicate any adverse effects of tiagabine during the double-blind phase at low doses (30 mg/day) or during the long-term open phase at doses up to 80 mg/day. The daily dosages in the long-term follow-up of this study were higher than in the previous reports.

Potential dose-related effects of tiagabine on cognition and mood were studied in a conversion-to-monotherapy study comparing doses of 6 mg/day and 36 mg/day tiagabine as monotherapy in previously uncontrolled epilepsy patients [56]. The study showed modest improvements in cognitive abilities and adjustment compared with baseline, during which the patients were receiving other AEDs. Tiagabine dose was related to the type of improvement, with the low dose more probably associated with improvement in adjustment and mood and the high dose probably associated with improvement in cognitive abilities. In the second conversion-to-monotherapy study, tiagabine was individually titrated to doses between 7.5 and 35 mg/day; in this study tiagabine did not produce cognitive or behavioural adverse effects compared with previous treatment using standard AEDs [57]. Successful tiagabine monotherapy seemed to be associated with improvement in simple psychomotor speed and to be associated with less fatigue compared with standard AEDs. A pooled analysis of two studies in newly diagnosed patients with partial seizures showed that after 52 weeks of tiagabine monotherapy (20–30 mg/day, $n = 42$) there were no detrimental effects on cognition. Results were similar to those recorded with carbamazepine monotherapy (400–800 mg/day, $n = 42$) [58].

Visual field investigations

Because of its action on GABAergic mechanisms, the question was raised as to whether tiagabine, like vigabatrin, can result in visual field abnormalities. However, there is no evidence that an increased risk of concentric visual field defects is a class effect of GABAergic drugs. The first ophthalmological study of 15 patients using tiagabine as monotherapy (mean daily dosage 21 mg, range 5–60 mg; mean duration of therapy 38 months, range 23–55 months) did not show any evidence of a relationship between visual field constriction and tiagabine treatment [59]. A larger cross-sectional study was set up in newly diagnosed patients with partial epilepsy receiving tiagabine, carbamazepine and lamotrigine as initial monotherapies [60]. Neurological and ophthalmological tests, including Goldmann and Humphrey perimetries, were performed. A neuro-ophthalmologist blindly reviewed all

visual charts. Seventy-three patients were included and completed the study. The population eligible for analysis included 68 patients, of whom 32 were treated with tiagabine (median duration, 25 months), 24 with carbamazepine (21 months), and 12 with lamotrigine (15 months). No patient treated with tiagabine showed a concentric visual field defect on Goldmann perimetry testing. No clinically relevant abnormalities in visual fields resembling those known with vigabatrin were detected, particularly in patients treated initially with tiagabine monotherapy. These findings support the evidence that tiagabine is not associated with retinal toxicity.

Idiosyncratic reactions

No idiosyncratic reactions have as yet been linked to the use of tiagabine [61]. No systematic abnormalities have been noted in haematology or blood chemistry values, and therefore there are no specific guidelines for routine monitoring of laboratory values during tiagabine treatment [30].

Teratogenicity

Teratogenic effects were seen in the offspring of rats exposed to maternally toxic doses of tiagabine, but not in animals receiving non-toxic dosages. Only very limited pregnancy data involving tiagabine, which show no clear evidence of teratogenicity, are available [62]. Therefore tiagabine cannot be recommended for women who are pregnant or at risk of becoming pregnant, and should be used only if the potential benefit justifies the potential risk to the fetus.

Place in current therapy

Tiagabine is indicated as add-on treatment for adults and children over 12 years with partial seizures with or without secondary generalization that cannot be satisfactorily controlled with other AEDs. The use of tiagabine in unclassified epilepsies and generalized epilepsy syndromes should be avoided, and off-label use in other indications is discouraged because of its potential to induce seizures and slow-wave activity in the EEG.

In most preclinical and clinical studies, the tiagabine dose was expressed in terms of milligrams of tiagabine hydrochloride. In the European Union, tiagabine is available as 2.5-, 5-, 10- and 15-mg tablets (content expressed as free base), and in the USA, Canada and Mexico it is available as 2-, 4-, 12-, 16- and 20-mg tablets (content expressed as tiagabine hydrochloride). A conversion factor of 0.91 can be used to convert the dose from tiagabine hydrochloride to tiagabine free base.

The current labelling in most countries states that the initial dosage is 7.5–15 mg/day, followed by weekly increments of 5–15 mg/day. In the USA, Canada and Mexico, the labelling suggests a lower initial dose of 4 mg/day, followed by weekly increments of 4–8 mg/day. Postmarketing studies and clinical experience to date suggest that tiagabine should be preferably started at a dose of 4 or 5 mg/day and gradually increased by weekly increments of 4 or 5 mg/day to minimize CNS-related adverse effects. Initial dosages can be given twice a day, but a switch to three times daily dosing is recommended with dosages above 30–32 mg/day. Tiagabine should always be taken with food, and preferably at the end of meals, to avoid rapid rises in plasma concentrations. Individual dosing four times daily may also be helpful, at least with higher doses.

Because tiagabine clearance is increased by enzyme-inducing AEDs, the usual initial target maintenance dosage in patients taking enzyme inducers is 30–32 mg/day, whereas in patients not taking enzyme-inducing drugs a lower initial maintenance dose of 15–16 mg/day is recommended [51]. The usual upper limit of maintenance dosages is 50–56 mg/day in patients taking enzyme-inducing drugs and 30–32 mg/day in patients not taking enzyme-inducing drugs. However, high daily doses of at least 70–80 mg are well tolerated in some individual patients. Patients taking a combination of inducing and non-inducing drugs (e.g. carbamazepine and valproate) should be considered to be enzyme induced. No AED should be suddenly withdrawn and, although there are no clinical data, it seems sensible to withdraw tiagabine gradually over at least 2–3 weeks [51].

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54 Topiramate

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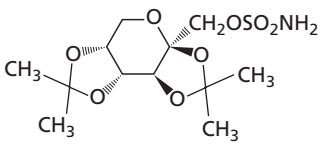

Primary indications	Adjunctive therapy or monotherapy in partial and secondarily generalized seizures. Also useful for Lennox–Gastaut syndrome and primary generalized tonic–clonic seizures
Usual preparations	Tablets: 25, 50, 100 and 200 mg. Sprinkle capsules: 15 and 25 mg
Usual dosages	Initial: 25 mg/day (adults), 0.5 mg/kg/day (children). Maintenance: 100–500 mg/day (adults), 2–9 mg/kg/day (children)
Dosing frequency	Twice a day
Significant drug interactions	Topiramate levels are lowered by carbamazepine, phenobarbital and phenytoin. Topiramate may increase serum phenytoin levels
Serum level monitoring	May be useful in selected cases
Reference range	5–20 mg/L
Common/important adverse effects	Dizziness, ataxia, headache, paraesthesia, tremor, somnolence, cognitive dysfunction, confusion, agitation, amnesia, depression, emotional lability, nausea, diarrhoea, diplopia, weight loss
Main advantages	High responder rates
Main disadvantages	Central nervous system adverse effects
Mechanisms of action	Blockade of sodium channels; potentiation of GABA-mediated inhibition at the $GABA_A$ receptor; reduction of excitatory actions of glutamate via the AMPA receptor; inhibition of high-voltage calcium channels; inhibition of carbonic anhydrase
Oral bioavailability	Close to 100%
Time to peak levels	2–4 h
Elimination	Partly by renal excretion and partly by oxidative metabolism
Volume of distribution	0.6–1.0 L/kg
Elimination half-life	10–30 h (varies with co-medication)
Plasma clearance	15–50 mL/kg/h (varies with co-medication)
Protein binding	13–17%
Active metabolites	None
Comment	A useful antiepileptic drug with relatively broad-spectrum efficacy

Introduction

Topiramate sulphamate is a second-generation antiepileptic drug (AED) that exerts antiepileptic activities by a combination of mechanisms of action, resulting in a relatively broad-spectrum efficacy in a variety of seizure types and epilepsy syndromes, partial and secondarily generalized seizures, some idiopathic generalized epilepsies and drop attacks associated with the Lennox–Gastaut syndrome. It is used in both adults and children, either as monotherapy or as an adjunctive agent.

Chemistry

Topiramate, 2,3 : 4,5-bis-*O*-(1-methylethylidene)-α-D-fructopyranose sulphamate, is a sulphamate-substituted monosaccharide,

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derived from D-fructose. Its empirical formula is $Cl_2H_{21}NO_8S$ and its molecular weight 339.37. It is a white crystalline powder with a bitter taste and a pK_a of 8.61 at 25°C. It is highly soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and stabilized at a pH of 9–10. It is also freely soluble in acetone, chloroform, dimethyl sulphoxide and ethanol. The solubility in water is 9.8 mg/mL at pH 6.7.

Pharmacology

Topiramate produces its anticonvulsant effects through inhibition of voltage-sensitive sodium and calcium channels, enhancement of γ-aminobutyric acid (GABA)-mediated activity and inhibition of kainate/α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)-type glutamate receptors (Table 54.1). It also is known to be an inhibitor of carbonic anhydrase due to similarities in structure to acetazolamide.

In cultured rat pyramidal neurones, topiramate decreases or abolishes sustained repetitive firing and spontaneous epileptiform burst firing in a dose-dependent and partially reversible manner [1]. These actions are consistent with an effect involving modulation of sodium and/or calcium channel conductance. Further studies of rat subicular neurones [2], cerebellar granule cells [3] and recordings from neocortical neurones [4] as well as studies with cultured mouse spinal neurones [5] have all provided evidence of an effect of topiramate on sodium channel conductance. Topiramate induces a hyperpolarization of the resting cell membrane potential and depresses the ability of cells to produce action potential bursts and spontaneous repetitive firing in response to depolarizing pulses. In addition, studies of whole-cell patch-clamp recordings from rat dentate granule cells also provide support for an inhibitory effect of topiramate on L-type high-voltage activated calcium channels [6].

A separate potential mechanism for the anticonvulsant action of topiramate is enhancement of GABA-mediated activity. Topiramate potentiates GABA-mediated chloride flux into neurones in a rapid and reversible manner [7] and the hyperpolarizing effects of topiramate on resting membrane potentials can be reversed using $GABA_A$ receptor antagonists [2]. Topiramate has also been shown to block the kainate-elicited membrane currents in cultured rat hippocampal pyramidal neurones induced by activation of the AMPA-type glutamate receptor [8]. However, it does not block membrane currents elicited through *N*-methyl-D-aspartate (NMDA) activation of NMDA receptors, which is relatively unique for an anticonvulsant drug.

Although topiramate has an inhibitory effect on carbonic anhydrase, this is a relatively weak action (acetazolamide is 10–100 times more potent). The inhibitory effect has been shown to be selective, affecting mostly two out of the six carbonic anhydrase isoenzymes (CAII and CAIV) [9]. This action is likely to be responsible for some of the adverse effects of topiramate, for example the increased incidence of renal stones and paraesthesia.

The multiple pharmacological actions of topiramate, in addition to contributing broad-spectrum efficacy in a variety of seizure types, are likely to be the reason that it also has a wide range of non-epilepsy indications (see section on non-epilepsy indications).

Table 54.1 Proposed mechanisms of action of topiramate.

Site	Action
Voltage-activated sodium channel	Limits sustained repetitive firing via state-dependent blockade of sodium channels
GABA receptor	Potentiates GABA-mediated neuroinhibition at a $GABA_A$ receptor site not modulated by benzodiazepines or barbiturates
Glutamate receptor subtypes (kainate/AMPA)	Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity
Calcium channels	Mild reduction of high-voltage activated calcium current amplitude
Carbonic anhydrase	Antagonizes isoenzymes, types II and IV

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

Pharmacokinetics

Overall pharmacokinetic features

Given within the normal dosing range, topiramate shows linear pharmacokinetics. The drug is rapidly and well absorbed from the gastrointestinal tract, with peak plasma concentrations occurring approximately 2–4 h after administration [10]. Ingestion with food delays topiramate absorption by about 2 h but the maximal plasma concentrations are unchanged for a given oral dose [11]. This is independent of whether the sprinkle or tablet formulation is used. Topiramate does not, therefore, need to be given in any fixed relationship to meal times.

Topiramate is widely distributed in all tissues and primarily to body water. Plasma protein binding is minimal (13–17%) [10]. A steady state is achieved in 4–6 days of regular dose administration in patients with normal renal function and the elimination half-life is in the order of 20–30 h in patients not taking enzyme inducers and 10–15 h in patients co-medicated with enzyme inducers. Apparent oral clearance (CL/*F*) values in non-induced and in enzyme-induced subjects are in the order of 15–30 and 30–50 mL/h/kg, respectively, [11,12].

Topiramate is excreted unchanged through the kidneys [13], although a fraction of the oral dose is metabolized, mostly by the cytochrome P450 (CYP) microsomal enzymes. In the absence of enzyme induction, the fraction of a topiramate dose excreted unchanged in the urine is in the order of 60–70%, but this decreases to about 40% in patients co-medicated with enzyme-inducing AEDs. At least 12 metabolites have been identified, formed by hydroxylation, hydrolysis, glucuronide or sulphate conjugation or cleavage of the sulphamate group [13]. None of these metabolites has antiepileptic activity.

Pharmacokinetics in special populations

Children

Topiramate CL/*F* values in infants older than 6 months and in children are 1.5- to 2-fold higher than in adults [12,14,15]. The increased clearance in children is inversely proportional to the child's age, presumably indicating an age-dependent change in the

rate of drug elimination. As in adults, topiramate CL/*F* values in children are, on average, about twofold higher in the presence of enzyme-inducing co-medication than with children not receiving enzyme inducers. For any given steady-state serum concentration to be achieved, the dosage of topiramate in milligrams per kilogram per day is expected to be higher in children than in adults. In fact, doses of up to 38 mg/kg/day have been used in some studies involving very young children, although such doses would not be usual in current clinical practice [14].

The elderly

Topiramate CL/*F* values are reduced by about 20% on average in elderly patients aged 65–85 years compared with non-elderly adults [12]. However, in patients older than 80, a greater decrease in clearance would be expected. Age-related changes in CL/*F*, together with interindividual variability in pharmacodynamic response, contribute to the need for individualized assessment of dosing in these patients.

Impaired renal function

Topiramate CL/*F* is reduced in patients with impaired renal function. This has been studied by giving a single 100-mg dose to patients with moderate (CL_{Cr} 30–69 mL/min) or severe ($CL_{Cr} \leq$ 30 mL/min) renal impairment and matching volunteers with normal renal function ($CL_{Cr} \geq 70$ mL/min) [16]. Topiramate CL/*F* was reduced by 42% in patients with moderate renal impairment and by 54% in patients with severe renal impairment compared with the volunteers with normal renal function. Therefore, topiramate doses should be reduced in patients with impaired renal function, according to the individual's creatinine clearance. In renal impairment, the time to achieve steady state is increased and dose adjustments should be made at intervals of 2 weeks rather than weekly, as is the practice for patients without renal impairment. With haemodialysis, however, topiramate CL/*F* significantly increases as topiramate is removed during the haemodialysis process. The clearance of topiramate during dialysis may be four to six times that of an individual with normal renal function. Patients undergoing haemodialysis may need additional dosage of topiramate for this reason.

Impaired hepatic function

Compared with healthy matched control subjects, topiramate CL/*F* was 26% lower and topiramate plasma concentrations were increased by 29% in five patients with moderate to severe liver impairment [17]. These changes were not considered clinically significant.

Drug interactions

Enzyme-inducing AEDs, such as phenytoin, phenobarbital and carbamazepine, induce the metabolism of topiramate. For example, concomitant carbamazepine therapy lowers the topiramate concentration by 40% when compared with topiramate monotherapy [18]. Relative to patients (both paediatric and adult) not receiving enzyme-inducing co-medications, those receiving enzyme-inducing AEDs exhibit a 1.5- to 2-fold increase in topiramate oral clearance (CL/*F*) and an approximately 50% reduction in the topiramate half-life. Dose adjustments to topiramate may therefore be required when phenytoin, phenobarbital or carbamazepine are added to or withdrawn from topiramate therapy.

In most patients, topiramate has no significant effect on the plasma concentrations of most concomitant AEDs. No change from baseline has been seen in the steady-state plasma concentrations of carbamazepine or its metabolite carbamazepine-10,11-epoxide with the addition of topiramate treatment [18]. When topiramate has been added to sodium valproate, a slight increase in valproic acid CL/*F* was noted together with a small decrease in plasma concentration, which did not appear to be clinically relevant [19]. Possible synergistic actions have been reported in animals and humans between lamotrigine and topiramate [20]. In children with partial-onset seizures, minor (about 10%) decreases in lamotrigine levels were noted in patients on topiramate compared with those who were given placebo [21].

Topiramate does not inhibit *in vitro* the CYP isoenzymes, except for some inhibition of CYP2C19 at very high concentrations (5–15 times the recommended clinical dosing regimen for adults) [22]. Inhibition of CYP2C19 does suggest that topiramate could inhibit phenytoin metabolism, but this isoenzyme is responsible for only 20% of phenytoin metabolism, so only a slight effect would be anticipated. *In vivo*, in a study of 12 patients on phenytoin treatment, nine patients had no change in plasma phenytoin levels when topiramate therapy was initiated, but an increase in phenytoin levels was noted in three patients [22]. Phenytoin metabolism might have been nearer saturation in these patients, so that a small inhibition of metabolism may have been sufficient to lead to the increase in the plasma phenytoin concentration. A dose reduction of phenytoin may therefore be required in some patients when topiramate is added, and phenytoin levels should be monitored in these patients.

Interactions between topiramate and other drugs, such as low-dose oral contraceptives, hydrochlorothiazide, metformin and risperidone, do occur, and this may require monitoring and/or dose adjustments (Table 54.2). Dose-dependent enzyme induction by topiramate leads to a decrease in the plasma concentration of ethinylestradiol, the oestrogen component of most oral contraceptives, but this interaction occurs only at relatively high topiramate dosages (>200 mg/day) and is not seen when lower doses are used [23–25]. The concomitant use of topiramate and other carbonic anhydrase inhibitors is not recommended.

Serum level monitoring

An overview of studies that assessed the relationship between serum topiramate concentrations and clinical response concluded that patients receiving therapeutic doses usually have levels in the range of 5–20 mg/L [26]. However, there is a considerable overlap between serum levels associated with an optimal response and those associated with toxicity. In recent years, there has been a trend to prescribe a lower dosage of topiramate than the doses used in earlier studies, and it is therefore likely that most patients achieving a good response do so at concentrations in the lower part of the range cited above. Although topiramate dose is usually adjusted on the basis of clinical response alone, monitoring serum concentrations may be of help in selected situations.

Table 54.2 Potential drug interactions with topiramate.

Co-medication	Interaction expected
Carbamazepine	Decreased serum levels of topiramate (see text)
Valproic acid	Possible minor decrease in the levels of valproic acid and topiramate. Possibly increase risk of hepatic encephalopathy
Phenobarbital/primidone	Decreased serum levels of topiramate (see text)
Phenytoin	Decreased serum levels of topiramate (see text) Increased serum phenytoin levels in some patients
Amitriptyline	Modest increase in serum amitriptyline and nortriptyline levels
Carbonic anhydrase inhibitors	Increased risk of renal calculi and hyperthermia
Central nervous system depressants	Increased risk of CNS depression
Digoxin	Minor decrease in serum digoxin levels
Haloperidol	Slight increase in serum haloperidol levels and a moderate increase in serum levels of the reduced haloperidol metabolite
Hydrochlorothiazide	Moderate increase in serum topiramate levels
Lithium	Slight decrease in serum lithium levels
Metformin	Moderate increase in serum metformin levels Decrease (extent unclear) in serum topiramate levels
Oral contraceptives	Decreased serum ethinylestradiol levels with doses of topiramate above 200 mg/day
Pioglitazone	Slight decrease in serum pioglitazone levels, and 60% decrease in serum levels of the active metabolite keto-pioglitazone
Risperidone	Modest decrease in serum risperidone levels, but no change in exposure to active moiety (risperidone + 9-hydroxy-risperidone)

Updated from ref. 25.

Efficacy

The antiepileptic efficacy of topiramate has been evaluated in numerous trials, both as a monotherapy and as an adjunctive therapy. Initial trials were undertaken in adults with refractory partial-onset seizures and high maintenance doses were used. With subsequent experience, it was recognized that greater adverse effects were reported when faster titration schedules and higher dosages were used, and further trials used substantially lower doses. Using slower titration schedules was also recognized to have no impact on the overall efficacy of topiramate [27–29]. The pivotal adjunctive therapy trials have demonstrated a reduction in frequency of seizures by at least 50% in 35–50% of subjects.

Monotherapy

The effectiveness of topiramate as monotherapy is clearly established. In a randomized double-blind dose comparison study in patients with newly diagnosed partial (with or without secondary generalization) or primarily generalized tonic–clonic seizures, topiramate used as monotherapy at a dose of 400 mg/day was associated with a greater proportion of seizure-free patients at 6 and 12 months ($P < 0.01$) than topiramate at a dose of 50 mg/day [30]. The first evaluation point with a significant difference ($P = 0.046$) favouring the higher dose was at day 14, when patients were receiving 100 or 25 mg/day. In an open trial of topiramate monotherapy in 692 patients with partial or generalized epilepsy who were treatment naive or had failed with prior treatment using one AED, 76% of patients were reported to have had a >50% reduction in seizure frequency with 44% of patients rendered seizure free [31]. The proportion of patients with partial seizures treated with topiramate for 6–7 months in these studies achieving seizure freedom was reported to be 40–82%, and the proportion of patients with generalized epilepsy achieving seizure freedom after a similar treatment period was 62–85%. Topiramate has therefore been demonstrated to be effective as monotherapy for both partial and generalized seizure types.

A number of comparative monotherapy trials have also been undertaken, providing data on the comparative efficacy of topiramate relative to other older and newer AEDs. In a randomized double-blind trial in 613 patients with newly diagnosed epilepsy, Privitera *et al.* [32] reported that the time to trial exit (due to inefficacy of treatment, adverse events, subject choice or loss to follow-up) was similar for topiramate, carbamazepine and valproate. In the secondary outcome measures (time to first seizure and proportion of seizure-free patients during the last 6 months of treatment), topiramate, carbamazepine and valproate also performed in a similar fashion. Two further comparative randomized non-blind trials conducted within the context of the SANAD (standard and new antiepileptic drugs) collaboration have been undertaken in patients with generalized or unclassified epilepsy [33] and in patients with partial epilepsy [34]. These flexible-dosage trials compared the efficacy and tolerability of valproate monotherapy (for patients with mostly generalized/unclassified epilepsy) against topiramate or lamotrigine [33], and the efficacy of carbamazepine (for patients mostly with partial seizures) against topiramate, gabapentin, lamotrigine or oxcarbazepine [34]. In the study of patients with generalized or unclassified epilepsy, topiramate was inferior to both valproate or lamotrigine in time to treatment failure (defined as 'time to cessation of treatment because of adverse events, inadequate seizure control or the addition of another AED'). Topiramate was more effective than lamotrigine, but not as effective as valproate in the time taken to achieve a 1-year period of remission from seizures. In the study of patients with partial epilepsy, topiramate was found to fare worse than carbamazepine for time to treatment failure (largely owing to adverse events). For time taken to achieve a 1-year remission from seizures, topiramate was not significantly different from carbamazepine or lamotrigine but for time to a 2-year remission from seizures carbamazepine was significantly better than topiramate.

Adjunctive therapy

A number of randomized placebo-controlled double-blind trials have demonstrated that topiramate is effective as an adjunctive therapy in adults and children with primary generalized tonic–clonic seizures [35], partial seizures with or without secondary generalization [21,36] and major seizures associated with the Lennox–Gastaut syndrome [37].

The efficacy of topiramate as adjunctive therapy for refractory partial-onset seizures was reviewed by the Cochrane collaboration [38]. The analysis included ten randomized placebo-controlled double-blind trials representing 1312 randomized participants. The relative risk for a 50% or greater reduction in

seizure frequency with topiramate compared with the placebo was 2.85 (95% CI 2.27–3.59), and dose regression analysis showed an increasing effect with increasing dose, but no advantage for doses over 300 mg or 400 mg per day. However, an individual study in adults with partial-onset seizures demonstrated a greater effect for topiramate dosages of 400 mg/day than dosages of 200 mg/day [36]. In a double-blind placebo-controlled trial in children with partial-onset seizures on one or two AEDs at the optimal dosage, addition of topiramate was effective in reducing the median seizure frequency from baseline (33% in the topiramate group versus 11% in the placebo group, $P = 0.03$), and there was a statistically significant greater proportion of children in the topiramate arm achieving >75% reduction in seizure frequency [21]. With a baseline seizure rate of 20 seizures per month, 5% of children receiving topiramate were seizure free during the 16-week study; however, no placebo-treated children were seizure free. No children discontinued topiramate treatment because of adverse events in the trial period. An open-label trial of large numbers of patients ($n > 400$) with partial-onset seizures and topiramate dosage adjustments according to clinical response have also demonstrated a reduction in median seizure frequency with topiramate therapy [29]. In this trial, topiramate tolerability was improved, with fewer discontinuations owing to adverse effects when dosages of concomitant AEDs were reduced.

In a randomized double-blind placebo-controlled trial in 80 adults and children with primary generalized tonic–clonic seizures [35], topiramate was titrated to target doses of approximately 6 mg/kg/day over 8 weeks and maintained for another 12 weeks. Median percentage reduction from baseline in primary generalized tonic–clonic seizure rate was 57% in the topiramate group compared with 9% for the placebo group ($P < 0.02$). Responder rates (proportion of patients with at least 50% reduction in primary generalized tonic–clonic seizures compared with baseline) were 56% and 20% for the topiramate and placebo groups, respectively ($P = 0.001$).

In a placebo-controlled trial in adult and paediatric patients with Lennox–Gastaut syndrome, topiramate was associated with a greater reduction in all major seizure types including drop attacks [37]. Patients receiving at least one standard AED had to have a confirmatory electroencephalogram (EEG) showing a slow spike–wave pattern with multiple seizure types including drop attacks (i.e. tonic or atonic seizures) and a history of atypical absences. Following randomization, topiramate was started at 1 mg/kg/day and increased at weekly intervals to 3 mg/kg/day and then 6 mg/kg/day. Stabilized dosages were maintained for an additional 8 weeks. In patients receiving topiramate, the median percentage of reduction in drop attacks was 15% compared with a 5% increase in patients receiving placebo ($P = 0.04$). The median percentage reduction in major motor seizures (drop attacks and tonic–clonic seizures combined) was 26% with topiramate treatment compared with a 5% increase with placebo ($P = 0.02$). The proportion of patients achieving at least 50% reduction in drop attacks was higher in the topiramate group than in placebo-treated patients (28% versus 14%, $P = 0.07$). With 33% of topiramate-treated patients and 8% of placebo-treated patients achieving at least 50% reduction in major motor seizures ($P = 0.002$), the effectiveness of topiramate against major motor seizures was similar to that previously reported with lamotrigine [39].

The benefits of topiramate on seizure reduction have also been documented in longer-term non-comparative open-label trials of topiramate as adjunctive therapy [40,41]. During long-term treatment in patients with generalized epilepsy [40], 16% of patients ($n = 96$) receiving topiramate for at least 6 months had no generalized tonic–clonic seizures for at least 6 months (mean topiramate dose 500 mg/day or 7 mg/kg/day for children). In patients treated for up to 2.5 years in this study ($n = 131$), 5% discontinued owing to inadequate seizure control and 8% discontinued owing to adverse events. Among patients who entered the long-term, open-label extension of the Lennox–Gastaut study [41], during which dosages of topiramate and concomitant AEDs could be adjusted according to response, drop attacks were reduced by at least 50% in 55% of patients receiving topiramate (mean dose 10 mg/kg/day) for at least 6 months ($n = 82$). Despite having had initially an average of 90 drop attacks per day, 15% of patients had no drop attacks for at least 6 months. Substantial reductions were also observed in atypical absence, myoclonic and tonic–clonic seizures. During follow-up for up to 3.4 years ($n = 97$), 12% of patients discontinued treatment owing to inadequate seizure control and 10% discontinued owing to adverse events. In an extension of the controlled trial of topiramate as adjunctive therapy in children with partial-onset seizures [21] with doses adjusted according to clinical response (mean 9 mg/kg/day) and a follow-up period of up to 2.5 years ($n = 83$), 14% of children were seizure free for at least 6 months and seizure frequency over the last 3 months of therapy was reduced in 57% of children. Six per cent of children discontinued treatment because of adverse events and 13% because of inadequate seizure control [42].

Patient retention rates provide another measure of long-term effectiveness. In a retrospective review of patients with refractory partial and/or generalized epilepsy in an adult tertiary referral centre [43,44] 1-year retention rates were 52% for topiramate, 46% for lamotrigine and 23% for gabapentin; 3-year retention rates were 30%, 29% and 10% respectively. Estimated retention rates at 5 years were 28% (topiramate), 12% (lamotrigine) and 2% (gabapentin). Perceived lack of efficacy resulted in treatment withdrawal in 19% of topiramate-treated patients compared with 39% of those receiving lamotrigine and 34% of those treated with gabapentin. Factors associated with long-term retention in topiramate-treated patients included higher maximal daily doses; younger age of epilepsy onset; prior exposure to fewer than two new AEDs; and treatment with no more than one concurrent AED [44]. A similar 1-year retention rate (55%) was reported for 174 patients receiving topiramate in a specialist regional epilepsy clinic [45]. When topiramate was substituted for another drug, the retention rate was 56% compared with 41% when topiramate was added to existing therapy ($P < 0.05$). Adverse events were more frequent in add-on patients than in substitution patients, which may reflect the lower tolerance of the drug when interactions occur with other AEDs. In total, nine (5%) patients became seizure free in the long term.

Studies in other paediatric epilepsy syndromes

In addition to trials that included children with partial-onset seizures, generalized tonic–clonic seizures and seizures associated with Lennox–Gastaut syndrome, there have also been a number

of open-label uncontrolled studies providing some information on the use of topiramate in children with other specific epilepsy syndromes, although the numbers of treated children in some of these studies are small.

West syndrome

The effectiveness of topiramate in West syndrome, characterized by infantile spasms, learning disability and hypsarrhythmia on EEGs, was evaluated in a pilot study in 11 infants refractory to previous AED therapy [46]. Topiramate dose was increased until seizures were controlled, adverse events limited further escalation or a maximum dose of 24 mg/kg/day was reached. The mean frequency of spasms was significantly reduced compared with baseline ($P = 0.003$). Nine patients (82%) had at least 50% reduction in spasms and five patients (45%) became spasm free. During long-term treatment, four out of the five spasm-free children remained spasm free for an average of 18 months (mean topiramate dose of 29 mg/kg/day). A subsequent study has reported success in the treatment of spasms using a combination of vigabatrin and topiramate [47]. In this study of four patients with cryptogenic infantile spasms, topiramate was added to vigabatrin when vigabatrin monotherapy had failed to control spasms or improve the background EEG. In all patients the addition of topiramate achieved rapid control of the spasms, and in three children the EEG also normalized and development progressed.

Childhood absence epilepsy

During a pilot study, children with typical absence seizures (documented as 3-Hz spike–wave on the EEG) who were untreated or taking only one AED were given topiramate. Among five children (6–11.5 years of age) completing the 6-week study, one previously untreated child became seizure free, two showed no improvement in clinical seizures or EEG activity and two showed an initial reduction in seizures, but seizures increased with higher topiramate dosages. With topiramate dose reduction to 6 mg/kg/day in these two children, seizure control improved (one became seizure free and one had at least 50% seizure reduction) [48].

Severe myoclonic epilepsy of infancy

The use of topiramate has also been reported in children with severe myoclonic epilepsy of infancy (Dravet's syndrome) [49]. This is a syndrome first described by Dravet, in which children initially present with prolonged, often lateralized, seizures in the first year of life with the emergence of myoclonus and developmental regression from the second year. Nieto-Barrera *et al*. [49] reported on 18 children with this syndrome who had topiramate added to their current therapy. At the time of entry in the study, these children had been treated with a mean of 6.7 different AEDs. The children were followed up for a mean of 10.5 months after the initiation of therapy with topiramate (range 6–18 months). At the end of the study 72% of patients had at least a 50% reduction in seizures, 50% at least a 75% reduction and 16.6% were seizure free. Other authors have also reported topiramate to be an effective medication for this syndrome [50].

Angelman's syndrome

In a report on the use of topiramate in five children with Angelman's syndrome, two children were seizure free on topiramate monotherapy after a mean of 8.8 months of observation [51].

Special epilepsy populations

Clinical reports suggest that topiramate is effective in controlling seizures in patients with learning difficulties [52,53]. Among 64 patients with refractory epilepsy who were learning disabled, 70% achieved at least 50% seizure reduction with topiramate adjunctive therapy. Sixteen patients (25%) became seizure free, including 10 who were receiving topiramate doses ≤200 mg/day [52]. In a group of 20 patients with intractable epilepsy (mixed seizures), mental retardation and developmental disabilities who were treated with topiramate adjunctive therapy, 69% had at least 50% seizure reduction and two (13%) were seizure free [53].

A recent 24-week pilot trial compared the efficacy and tolerability of topiramate as add-on or monotherapy in 77 elderly patients (mean age, 68 years) with one or more partial-onset seizures in the previous 6 months [54]. Patients were randomized to receive either 50 or 200 mg/day topiramate, titrated by 25 mg/day per week to target or maximum tolerated dose. Seizure control was similar with the two dosages when the drug could be used as a monotherapy, but 200 mg/day was more effective in patients requiring adjunctive therapy. A total of 14 patients (seven in each group) discontinued topiramate use as a result of adverse events. The authors concluded that their findings support the practice of using low-to-moderate dosages of AEDs in older adults.

Non-epilepsy indications

Migraine

Topiramate has now been established as a prophylactic treatment for migraine. Three randomized, double-blind, placebo-controlled trials in over 1500 patients have shown that topiramate decreases the frequency of migraine attacks with a good safety profile [55]. The optimal maintenance dosage for this indication is usually 100 mg/day. Adverse events reported in migraine patients are generally mild, with paraesthesia, fatigue, nausea and impaired concentration being those most commonly reported. Treatment is usually given for 6–12 months, but it is recognized that the antimigraine effect of topiramate can outlast the duration of therapy. In fact, sustained benefit (reduced migraine frequency and better quality of life) have been reported in patients after discontinuation of topiramate treatment [56].

Psychiatric disorders

Although there are a number of open clinical studies reporting that topiramate can be of benefit in a range of psychiatric disorders, including refractory bipolar mania, refractory bipolar depression, mood disorders, post-traumatic stress disorder and substance abuse, controlled studies are few in number. In some double-blind placebo-controlled trials that have been undertaken, there has been no demonstrable effect of topiramate therapy on bipolar I disorder [57], bipolar type schizoaffective disorder [58], acute mania [59] or post-traumatic stress disorder [60].

Neuropathic pain

Like other AEDs, topiramate may have a role in the treatment of neuropathic pain. In one double-blind, randomized, two-period

cross-over trial of topiramate (50–400 mg/day) with diphenhydramine as an active placebo in patients with chronic lumbar radicular pain, global pain scores were better during topiramate therapy ($P < 0.005$), even though many adverse effects and dropouts were reported [61]. A beneficial effect of topiramate was not observed in patients with painful diabetic neuropathy [62].

Obesity

A placebo-controlled trial of topiramate as a treatment of binge eating disorders and body mass index between 30 and 50 kg/m^2 has demonstrated that topiramate has an effect in reducing binge eating and body mass index [63,64]. In addition to reducing weight, topiramate therapy has been associated with improvement in blood pressure and glucose homeostasis in obese patients [65]. Topiramate has also been evaluated in patients with obesity and type 2 diabetes mellitus, in whom it was demonstrated to be effective (when combined with lifestyle alterations) in producing weight loss and improvement in glucose homeostasis [66]. In patients with bipolar-type schizoaffective disorder, topiramate has been shown to reduce weight and body mass index, although without a significant effect on the underlying bipolar disorder [58]. The positive effects of the drug on body weight, however, should be weighed carefully against the risk of adverse effects.

Adverse effects

The efficacy of any AED has to be balanced with the possible adverse effect profile. Early evidence of topiramate's adverse effects came from randomized controlled adjunctive therapy trials, which suggested that the most troublesome adverse effects were CNS related. In these investigations, titration was over a 4- to 6-week period, and adverse effects were influenced by the population studied as well as the specific titration rates and dosages used. Subsequent open-label extensions and observational studies contributed further information on the adverse effect profile of topiramate as well as on its long-term usage.

Central and peripheral nervous system-related adverse effects that occur with topiramate include cognitive effects (confusion, psychomotor slowing, difficulties with concentration and attention, memory problems and speech and language problems, especially word-finding difficulties and reduced verbal fluency), psychiatric or behavioural disturbance (anxiety, depression, mood changes and rarely psychotic symptoms), somnolence, fatigue and other effects such as dizziness, paraesthesia, incoordination, vertigo and involuntary movements. Cognitive adverse effects can occur in isolation. Many of these effects are more common with rapid titration rates and higher initial dosages [27]. Other adverse effects include metabolic acidosis, renal calculi, hypohidrosis, loss of appetite, weight loss, diarrhoea and ophthalmological adverse effects, including blurred vision, diplopia, acute angle-closure glaucoma and ciliochoroidal detachment.

Although initial trials reported a wide range of troublesome CNS effects, in longer-term trials using individualized dosages and titration rates representative of current clinical practice [31,67], the most frequently reported adverse effects were mainly restricted to somnolence and fatigue, paraesthesia, headache, anorexia and weight loss. Flexibility in topiramate dosing rates and in adjustments of the dose of concomitant AEDs has been associated with improved tolerability [30] with a lower proportion of patients exiting the study because of adverse events. There are few head-to-head clinical trials comparing the tolerability of topiramate with other AEDs, but one comparative double-blind trial in patients with newly diagnosed epilepsy found no significant difference in the proportion of patients discontinuing treatment with either topiramate, valproate or carbamazepine [32]. In the arm of the SANAD monotherapy trial that included mostly patients with partial seizures [34], the proportion of patients experiencing at least one adverse event was 53% for topiramate, 48% for carbamazepine and 45% for lamotrigine. In the arm that included mostly patients with generalized or unclassified epilepsy [33], the proportion experiencing at least one adverse event was 45% for topiramate, 36% for valproate and 37% for lamotrigine. In both arms of the trial, discontinuation rates owing to adverse effects were higher for patients receiving topiramate than for those randomized to the other AEDs. Adverse events reported in children are similar to those reported in adults, and, as in adults, adverse events are more prevalent with faster rates of titration and polytherapy.

Central nervous system adverse effects

A clear association has been shown between topiramate and cognitive decline in a study that measured cognitive scores in patients with refractory epilepsy during and after adjunctive topiramate therapy, and in a further group of patients assessed before and during topiramate therapy [68]. There appears to be a specific profile for topiramate-related cognitive adverse effects, with a particular impact on working memory, short-term verbal memory, language skills (including verbal fluency), verbal IQ, attention/concentration, processing speed, complex visuomotor ability and perception [68–75]. In most individuals it appears that these effects can be minimized by a slow, cautious introduction of the medication and by minimizing polytherapy. However, there appears to be a small proportion of patients who are extremely sensitive to these adverse effects and are unable to tolerate topiramate regardless of how cautious the introduction is. It is recognized that the effects of topiramate on cognition may appear even at low doses and persist with long-term treatment [69], but cognitive deficits have been demonstrated to be reversed on withdrawal of topiramate [75].

Topiramate can also have a negative effect on mood, with dose-dependent mood lability and affective disorder reported in around 10% of patients [76]. Symptoms of psychosis have been seen in some patients [76], but it is not clear if the incidence is greater than expected in populations with severe epilepsy.

Paraesthesiae are frequently reported in adult patients on topiramate, and are likely to be related to carbonic anhydrase inhibition.

Metabolic acidosis, bone effects and renal calculi

There are a number of adverse effects of topiramate, in addition to paraesthesiae, that are probably related to inhibition of carbonic anhydrase. These include an association with hyperchloraemic non-anion gap metabolic acidosis (as a result of decreased serum bicarbonate), renal calculi and hypohidrosis. These effects are more commonly reported in children [77,78] but they also occur in adults [79].

A moderate reduction in bicarbonate and hence a mild compensated metabolic acidosis is seen in most children taking topiramate. Metabolic acidosis generally occurs early in treatment and is usually mild and asymptomatic, and reverses with treatment discontinuation. Markedly low serum bicarbonate levels can occur, especially in young infants and also in patients who may already be predisposed to acidosis, for example those on the ketogenic diet. Such patients should be observed for clinical symptoms of acidosis which might necessitate discontinuation of treatment with topiramate. Acute treatment with bicarbonate is usually not required.

Chronic metabolic acidosis can result in osteomalacia and/or osteoporosis, reduced growth in children and renal calculi. Therefore, patients with persisting metabolic acidosis may warrant review of their treatment or initiation of oral bicarbonate treatment, especially if other conditions exist which predispose to any of these complications. The formation of renal calculi has been reported in around 1.5% of adults taking topiramate, with a higher incidence in men (as for renal calculi formation in the general population). Adequate hydration is important in patients at risk of renal calculi formation. If renal calculi occur, medical treatment may be effective and calculi are passed spontaneously in two-thirds of those affected.

Weight loss

Topiramate is associated with a decrease in weight in over 80% of patients, with those who are more overweight experiencing greater weight loss during ongoing therapy [80–82]. The mechanism of weight loss is unknown and is not completely explained by anorexia and reduced caloric intake as weight loss continues even when caloric intake returns to normal [80]. Mean weight decrease seen with topiramate is in the region of 2–7% and occurs early in the treatment with a plateau by 15–18 months [83].

Ophthalmological adverse effects

A range of ocular adverse effects have been reported, including blurring of vision, diplopia, acute angle-closure glaucoma, acute myopia and ciliochoroidal detachment [84,85]. Some of these effects do not appear to be dose related.

Ocular adverse effects are rare and appear to be due to an idiosyncratic reaction that causes ciliochoroidal effusion, anterior displacement of the lens and, subsequently, secondary acute angle-closure glaucoma with increased intraocular pressure. If this occurs, it is usually early in the treatment (within the first month) and resolves with discontinuation of therapy.

Hepatic adverse effects

Hyperammonaemia, with or without encephalopathy, has been reported following concomitant therapy with topiramate and valproate [86,87]. In most cases the manifestations resolved with discontinuation of either topiramate or valproate. Patients who might be predisposed to hyperammonaemia, such as those with inborn errors of metabolism or reduced hepatic mitochondrial activity, may be at higher risk of liver dysfunction with topiramate and/or valproate.

Adverse effects in children

Adverse effects reported in children have been similar to those seen in adults, with CNS effects and anorexia/weight loss being troublesome effects often reported by parents. Paraesthesia appears to be less prevalent, but it may be under-reported in this patient group and has been considered as a possible cause of agitation in some learning-disabled children.

Overall, the most common adverse events recorded in paediatric randomized trials include somnolence, anorexia, fatigue, dizziness, psychomotor slowing, speech difficulties and concentration difficulties. Although children may be particularly at risk of metabolic acidosis, renal calculi are rarely reported in paediatric populations.

Local carbonic anhydrase inhibition at the level of the sweat glands is the proposed mechanism for topiramate-related hypohidrosis and hyperthermia, seen especially in children [88,89]. In one study, 9 out of 14 patients on topiramate were found to have reduced sweating [89], the majority being children. Three of these patients had symptoms of heat intolerance. Patients on topiramate, especially children, should therefore be monitored for increased body temperature during hot weather and/or vigorous exercise.

Adverse effects during pregnancy/puerperium

Topiramate has been found to be teratogenic in animals, but its possible effects on the human fetus is unknown. With the advent of pregnancy registers, data on the comparative human teratogenic risks of AEDs are accumulating, but the relative or exact risk for topiramate is unknown. Although there are case reports of hypospadias occurring in the newborn in conjunction with topiramate exposure in pregnancy, in these cases topiramate was used in combination with carbamazepine and/or lamotrigine.

The concentrations of topiramate have been measured in plasma and breast milk in a small number of women with epilepsy during pregnancy and lactation [90]. Levels of topiramate in umbilical cord plasma and maternal plasma were almost identical, suggesting extensive placental transfer of the drug. The mean milk/maternal plasma concentration ratio was 0.86 (range 0.67–1.1) 2–3 weeks after delivery, and this ratio was similar at 1 and 3 months post partum. Low levels of topiramate were found in the blood of the breastfed infants, and none had any observed adverse effects.

Place in current therapy

Topiramate has proved to be an effective broad-spectrum agent in the treatment of epilepsy. Efficacy has been demonstrated against most seizure types in placebo-controlled and open-label trials, with little evidence of aggravation of seizures. However, it is likely that lower doses are more effective than those initially utilized in randomized trials. Efficacy with relatively good tolerability has also been demonstrated in monotherapy.

Topiramate has a particular place in the treatment of resistant focal seizures and symptomatic generalized epilepsies, where certain AEDs have been shown to be ineffective or contraindicated. It may be of particular benefit in patients who are overweight or obese, and in patients with epilepsy who also suffer

from migraine. Adverse effects may be minimized or avoided by reducing concomitant medication and by cautious titration.

Because of the risk of adverse effects, topiramate should be introduced at a low dose (0.5 mg/kg/day in children, or 25 mg/day in adults), and titration upwards should be slow (initially, no more than 0.5 mg/kg per week in children, or 25 mg/day per week in adults). Efficacy should be reviewed at 50 mg or 2 mg/kg/day, although much higher doses can sometimes be required and tolerated. There remains, however, a small group who are unable to tolerate the medication, regardless of the dose or rate of titration used.

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55 Valproate

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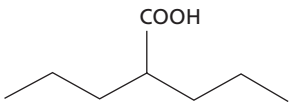

Primary indications	First-line therapy of idiopathic generalized epilepsies. First-line or adjunctive therapy of cryptogenic or symptomatic generalized epilepsies. Valuable but not generally first-line therapy for partial seizures
Usual preparations	Enteric-coated tablets, 200, 500 mg; crushable tablets, 100 mg; capsules, 150, 300, 500 mg; solution or syrup, 200 mg/5 mL, 250 mg/5 mL; sustained-release tablets, 200, 300, 500 mg; sustained-release microspheres, sachets, 100, 250, 500, 750, 1000 mg; divalproex tablets, 125, 300, 500 mg (as valproic acid equivalents); divalproex tablets delayed release, 125, 250, 500 mg (as valproic acid equivalents); divalproex sprinkles, 125 mg (as valproic acid equivalents); divalproex tablets extended release, 250, 500 mg (as valproic acid equivalents); solution for intravenous injection, 100 mg/mL
Usual dosages	Initial: 400–500 mg/day (adults); 15 mg/kg/day (children). Maintenance: 500–2500 mg/day (adults); 20–40 mg/day (children under 20 kg); 20–30 mg/kg/day (children over 20 kg). Higher doses may be needed, particularly in patients co-medicated with enzyme-inducing drugs
Dosing frequency	Two or three times a day. Some extended/sustained-release formulations may be used once daily, particularly in patients expected to have half-lives in the upper range
Significant drug interactions	Enzyme-inducing drugs and imipenem antibiotics reduce serum valproic acid levels. Felbamate, stiripentol, isoniazid and other drugs may increase valproic acid levels. Valproic acid inhibits the metabolism of a number of drugs, most notably phenobarbital, lamotrigine and rufinamide. Valproic acid displaces phenytoin from plasma protein binding sites and may inhibit phenytoin metabolism at the same time
Serum level monitoring	Dosage usually can be adjusted on the basis of clinical response, but monitoring serum valproic acid levels may be useful in selected cases
Reference range	50–100 mg/L
Common/important adverse effects	Tremor, sedation, asthenia, encephalopathy, extrapyramidal symptoms, nausea, vomiting, hyperammonaemia, weight gain, polycystic ovary syndrome, hair loss, platelet and coagulation disorders, liver toxicity, pancreatitis, teratogenic effects (including spina bifida)
Main advantages	Unsurpassed efficacy in most generalized epilepsy syndromes. Broad-spectrum efficacy in different seizure types
Main disadvantages	Weight gain, severe liver toxicity (particularly in children), teratogenicity
Mechanism of action	Not well defined, but clearly multifactorial. Effects include potentiation of GABAergic inhibition and attenuation of glutamatergic excitation

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Oral bioavailability	>90%
Time to peak levels	1–10 h (dependent on formulation and, with some formulations, concomitant food intake)
Elimination	Oxidation and glucuronide conjugation
Volume of distribution	Approximately 0.2 L/kg
Elimination of half-life	8–16 h in adults and 6–15 h in children (the shortest values in patients co-medicated with enzyme-inducing drugs). Neonates have longer half-lives
Plasma clearance	6–20 mL/h/kg in adults and 10–30 mL/h/kg in children (the highest values in patients co-medicated with enzyme-inducing drugs)
Protein binding	70–95% (decreasing with increasing serum concentration)
Active metabolites	None of major therapeutic relevance. The metabolite 4-ene-valproic acid may contribute to idiosyncratic adverse effects
Comment	A very valuable antiepileptic drug, particularly in the management of generalized epilepsies

Introduction

Valproic acid, or valproate, has been in clinical use for the treatment of epilepsy for more than 40 years. During this period, it has clearly established itself as one of the major antiepileptic drugs (AEDs). Over time, it became evident that valproic acid was the first and, until the 1990s, the only drug with a very broad spectrum of activity against different seizure types, both generalized and focal. It was also soon recognized that it had a relatively low sedative effect. In addition to being the first drug to be highly effective against virtually all primarily generalized seizure types, such as absence seizures, myoclonic seizures and generalized tonic–clonic seizures, valproic acid also was shown to have variable degrees of effectiveness in the treatment of partial seizures, the Lennox–Gastaut syndrome, infantile spasms, neonatal seizures and febrile seizures. Because of this, valproic acid assumed a particularly important role in the treatment of paediatric epilepsies. It is currently a first-line drug in all forms of primary (idiopathic) generalized epilepsy. Lamotrigine has been considered as an alternative for this indication, but its efficacy has not matched that of valproic acid, and it can exacerbate myoclonic seizures, which has not been reported for valproic acid. However, valproic acid does have several adverse effects, some of which can be bothersome or serious, whereas the only potentially bothersome or serious adverse effect of lamotrigine is a rash that may evolve to Stevens–Johnson syndrome.

In addition to its place in the treatment of epilepsy, valproic acid has gained acceptance in the treatment of conditions that will not be included in this chapter, such as affective disorders in psychiatry and the prophylaxis of migraine headaches. It has also been suggested that valproic acid may be effective in the treatment of Sydenham's chorea. The only limitation to the use of valproic acid has been its association with some undesirable and potentially serious side-effects.

Chemistry

Valproic acid, *N*-dipropylacetic acid, is a short-chain branched fatty acid with a molecular weight of 144.21. Chemically, valproic acid differs from all other known AEDs.

Valproic acid itself is a colourless liquid with a low solubility in water. Sodium valproate (molecular weight 166.19) is a highly water-soluble and highly hygroscopic white crystalline material. Other preparations include magnesium valproate, a divalproate salt and sodium hydrogen divalproate (divalproex sodium), a stable coordination compound composed of equal parts of valproic acid and sodium valproate.

Pharmacology

Activity in animal models of seizures and epilepsy

The discovery of the anticonvulsant effect of valproic acid was serendipitous, when it was used as a solvent for compounds being tested in an animal model of seizures [1]. Several animal models have been used to investigate the antiepileptic activity of valproic acid. Demonstrated activities include protection against maximal electroshock–induced seizures, seizures induced chemically by pentylenetetrazole, bicuculline, glutamic acid, kainic acid, strychnine, ouabain, nicotine and intramuscular penicillin, seizures induced by kindling, and spontaneously occurring seizures in genetic models of generalized epilepsy such as the GAERS (genetic absence epileptic rat of Strasbourg) rat. This broad spectrum of efficacy in animal models suggests that valproic acid is effective in both preventing the spread and lowering the threshold of seizures, and this is consistent with its broad spectrum of antiepileptic activity in humans.

Mechanisms of action

The elucidation of the mechanism of action of valproic acid has been the object of extensive studies. At the cellular level, several

effects of valproic acid have been demonstrated, but the mechanism underlying its antiepileptic action has not been precisely identified. It may be that more than one mechanism is involved, and none of the identified actions has been widely accepted as the predominant relevant mechanism [2].

Valproic acid has been shown to raise brain levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). This may occur through inhibition of GABA transaminase, the first step in GABA deactivation, through inhibition of succinic semialdehyde dehydrogenase, the second step in GABA deactivation, or through an increase in the activity of glutamic acid decarboxylase, an enzyme involved in the synthesis of GABA. However, these changes occur at much higher than usual therapeutic doses and their time-course lags behind the anticonvulsant effect. Therefore, it does not appear likely that elevation of GABA is the predominant mechanism of the antiepileptic effect of valproic acid. It has also been demonstrated that, in addition to its effect on GABA levels, valproic acid can reduce sustained repetitive high-frequency firing by blocking voltage-sensitive sodium channels [3], although the relevance of this effect at therapeutic concentrations is unclear [2], or by activating calcium-dependent potassium conductance. Valproic acid has also been found to reduce the release of γ-hydroxybutyrate, to decrease brain levels of the excitatory amino acid aspartate in mice and to decrease the expression of the glutamate transporter-1 in the rat hippocampus [4]. To what extent these actions contribute to the clinical effects of valproic acid remains unknown.

Pharmacokinetics

Rate and extent of absorption

Oral preparations of valproic acid have a virtually complete bioavailability when compared with the intravenous route. Rectal administration of valproic acid syrup was shown to have the same bioavailability as the oral preparation. The bioavailability of valproic acid suppositories was found to be 80% in volunteers, when compared with oral syrup. Administration of valproic acid suppositories was well tolerated for several days in a study in patients treated chronically with valproic acid, and the bioavailability was the same as for the oral preparations [5]. Available evidence suggests that there is no need for a dosage change or a change in regimen when oral valproic acid administration is transiently replaced by rectal administration. Compared with other divalproex oral preparations, the oral bioavailability of the divalproex extended-release preparation is 8–20% lower [6].

The rate of absorption of valproic acid is quite variable following oral administration, depending on the formulation. Syrup and uncoated regular tablets or capsules administered orally are rapidly absorbed, and peak serum drug levels are achieved within about 2 h. The purpose of the enteric coating of tablets is to prevent the gastric irritation associated with release of valproic acid in the stomach. Absorption from enteric-coated tablets is delayed until the tablet reaches the alkaline environment of the duodenum, but absorption is rapid once it begins. The onset of absorption from enteric-coated tablets varies as a function of the state of gastric emptying at the time of ingestion, and when the tablets are co-administered with food, peak serum drug levels may be reached only several hours after intake. Because of this delayed absorption, serum levels of valproic acid in patients taking valproic acid enteric-coated tablets continue to decrease for 2 or more hours after drug ingestion, until the absorption begins and exceeds the rate of elimination. Therefore, the assumed 'trough levels' before the morning dose are not the lowest valproic acid levels of a 24-h cycle. The lowest levels may actually occur in the late morning or early afternoon [7]. In 12 children, the absorption of enteric-coated sprinkles was compared with the absorption of valproic acid syrup, and no difference in overall bioavailability was found between the two formulations. The absorption of valproic acid was slower with the sprinkles than with the syrup, with an average time to maximal valproic acid concentrations of 4.2 h after ingestion of sprinkles and 0.9 h after intake of the syrup [8]. Sustained- and extended-release formulations are also available which ensure a smoother absorption profile and minimize fluctuations in serum valproic acid levels during a dosing interval. Most sustained-release formulations are suitable for twice-daily dosing, and some may also be feasible for once-daily administration.

Distribution

Valproic acid has a relatively small volume of distribution (0.13–0.19 L/kg in adults and 0.20–0.30 L/kg in children). This implies that the affinity of valproic acid for binding sites outside the plasma compartment is relatively lower than the affinity for binding sites on plasma proteins. The plasma protein binding of valproic acid is indeed high (about 70–95%), and it is saturable at therapeutic concentrations. Accordingly, the free (unbound) fraction of valproic acid increases as the total concentration increases. For instance, the average unbound fraction of valproic acid in adults was reported to be only 7% at 50 mg/L and 9% at 75 mg/L, increasing to 15% at 100 mg/L, 22% at 125 mg/L and 30% at 150 mg/L [9]. Using these unbound fraction values one can calculate that, with a threefold increase in total serum valproic acid concentration from 50 to 150 mg/L, the unbound concentration would increase more than 10 times, from 3.5 mg/L to 45 mg/L.

Since valproic acid shows restrictive clearance (i.e. total plasma clearance is directly proportional to the drug's unbound fraction), its saturable binding to plasma proteins implies that the relationship between the daily dose and the total concentration of valproic acid in serum is curvilinear, with relatively smaller increases in concentrations at higher doses. However, the relationship between dose and steady-state unbound serum valproic acid concentration (which is the fraction responsible for the pharmacological effect) is substantially linear.

Elimination

In the absence of enzyme-inducing drugs, the elimination half-life of valproic acid in adults is 13–16 h. Shorter values, averaging about 9 h, are recorded in patients co-medicated with enzyme-inducing drugs [10].

The elimination of valproic acid occurs virtually entirely by metabolism. The biotransformation in humans follows several pathways, including glucuronidation, beta-oxidation, hydroxylation, ketone formation and desaturation. The formation of double bonds can result from beta-oxidation as well as from

desaturation. Valproic acid glucuronide and 3-oxo-valproic acid are by far the most abundant metabolites, representing about 40% and 33%, respectively, of the urinary excretion of a valproic acid dose [11]. Anticonvulsant activity that is similar in potency to that of valproic acid itself was demonstrated for two desaturated metabolites of valproic acid, 2-ene-valproic acid and 4-ene-valproic acid, but these metabolites are present in serum at very low concentrations.

Because 2-ene-valproic acid undergoes delayed but significant accumulation in the brain, and is cleared more slowly than valproic acid itself, its formation may provide a possible explanation for the apparent dissociation between the time courses of valproic acid concentrations in plasma and the onset of antiepileptic activity. It appears that 2-ene-valproic acid does not possess the pronounced embryotoxicity and hepatotoxicity of 4-ene-valproic acid, and might thus represent a better AED than valproic acid itself.

The strongly hepatotoxic metabolite 4-ene-valproic acid is produced under the action of cytochrome P450 enzymes. The activity of these enzymes is induced by other AEDs such as phenobarbital, phenytoin and carbamazepine [11], and this may explain the increased risk of hepatotoxicity in patients receiving these drugs together with valproic acid [12]. However, elevation of 4-ene-valproic acid levels has not been clearly documented in patients with valproic acid hepatotoxicity, or in conjunction with short-term adverse effects or hyperammonaemia.

Pharmacokinetics in special groups

Children and newborns

Children have slightly shorter valproic acid half-lives than adults. Cloyd *et al*. [13] found an average half-life of 11.6 h in children on monotherapy and 7.0 h with polytherapy involving enzyme-inducing AEDs. Clearance values are also higher in children (20–30 mL/h/kg) than in adults (6–20 mL/h/kg). As a result, dosage requirements on a milligram per kilogram basis are generally higher in children than in adults.

Newborns eliminate valproic acid slowly, with half-lives that are longer than 20 h and up to 40 h [14]. The free (unbound) fraction of valproic acid is also higher in newborns.

Old age

Reduced plasma protein binding of valproic acid is reported in the elderly, in relation with a physiological reduction in plasma albumin levels. Compared with non-elderly adults, patients in old age also have a moderately reduced clearance of unbound drug, resulting in higher serum unbound valproic acid concentrations for equal dosages. Partly as a result of this, valproic acid dosage requirements tend to be lower in the elderly.

Pregnancy

During pregnancy, there is often a decrease in total serum valproic acid levels and an increase in unbound fraction. Therefore, despite the decrease in total serum concentrations, unbound valproic acid concentrations are generally relatively stable during pregnancy, and may even be slightly increased at the time of delivery. Breast milk contains 1–10% of the mother's plasma concentration, and breastfed infants have been found to have serum valproic acid concentrations of between 4% and 12% of their mothers' serum levels.

Disease states

Liver cirrhosis may lead to decreased plasma protein binding and decreased clearance of unbound valproic acid. Renal disease seems to have little or no impact on the pharmacokinetics of unbound valproic acid, although protein binding may again be reduced.

Drug interactions

Three pharmacological properties of valproic acid determine its involvement in several pharmacokinetic interactions [15]: (1) the metabolism of valproic acid is sensitive to enzymatic induction; (2) valproic acid itself can inhibit the metabolism of other drugs and (3) valproic acid can displace other drugs from serum proteins, because it has itself a high affinity for serum proteins. Pharmacodynamic interactions may also occur.

Effect of other drugs on valproic acid pharmacokinetics

There is ample documentation that enzyme-inducing AEDs, such as carbamazepine, phenytoin, phenobarbital and primidone, decrease serum valproic acid levels when administered concomitantly. In particular, valproic acid levels are lowered significantly, usually by at least one-third to one-half, by the addition of both carbamazepine and phenytoin. In children, these interactions can be particularly pronounced, resulting in valproic acid level reductions of 50% or more. Conversely, when other drugs were discontinued in children receiving enzyme-inducing AEDs, valproic acid levels rose 122% after withdrawal of phenytoin, 67% after withdrawal of phenobarbital, and 50% after withdrawal of carbamazepine [16]. If the same serum level of valproic acid is to be maintained when an enzyme-inducing drug is added or withdrawn, the dose of valproic acid has to be increased or decreased, respectively, by a factor of about two. The addition of lamotrigine may decrease valproic acid levels by about 25%, and a decrease in serum valproic acid levels may also be caused by oestrogen-containing contraceptive steroids. Valproic acid levels can also be decreased to a clinically relevant degree by the carbapenem group of antibiotics, particularly meropenem, although the mechanisms underlying this interaction are unclear [17]. Valproic acid levels may also be lowered by rifampicin and by the anti-HIV agent ritonavir (Table 55.1).

Unlike enzyme inducers, felbamate acts as an enzyme inhibitor and raises the serum levels of valproic acid. At a felbamate dose of 1200 mg/day, the increase in valproic acid levels was found to be 28%, and it was 54% at a felbamate dose of 2400 mg/day [18]. Among AEDs, , stiripentol and clobazam (in addition to felbamate) have also been reported to reduce the clearance and to elevate the serum levels of valproic acid. Among other drugs, fluoxetine, isoniazid and acetylsalicylic acid can also increase serum valproic acid levels. Because acetylsalicylic acid also displaces valproic acid from plasma protein binding sites, changes in total serum valproic acid levels in patients started on acetylsalicylic acid co-medication may underestimate the increase in the

Table 55.1 Pharmacokinetic interactions with valproic acid.

Other drugs decreasing serum valproic acid levels

The clearance of valproic acid is increased and the serum levels of valproic acid are lowered by the addition of the following drugs (discontinuation of these drugs has an opposite effect):

Antiepileptic drugs: phenytoin, carbamazepine, phenobarbital, primidone, lamotrigine

Others: imipenem antibiotics, ritonavir, rifampicin, steroid contraceptives

The clearance of valproic acid is decreased and the serum levels of valproic acid are increased by the addition of the following drugs (discontinuation of these drugs has an opposite effect):

Antiepileptic drugs: felbamate, stiripentol, clobazam

Others: acetylsalicylic acid (increase in unbound serum valproic acid), fluoxetine, isoniazid

Valproic acid increasing the serum levels of other drugs

Valproic acid decreases the clearance and increases the serum levels of the following drugs (discontinuation of valproic acid has an opposite effect):

Antiepileptic drugs: phenobarbital, lamotrigine, ethosuximide, carbamazepine-10,11-epoxide, phenytoin (increase in unbound serum phenytoin), rufinamide, felbamate, lorazepam

Others: amitriptyline and nortriptyline, zidovudine and the calcium channel blocker nimodipine

Plasma protein-binding interactions resulting in higher unbound drug fraction

Unless additional mechanisms are operating, these interactions generally result in decreased total concentration of the displaced drug, without affecting its unbound concentration and pharmacological effect

Valproic acid displaces phenytoin (and may also inhibit phenytoin metabolism)

Aspirin, salicylic acid, naproxen, diflunisal, tolmetin and ibuprofen displace valproic acid. Aspirin and salicylic acid may also inhibit valproic acid metabolism

levels of serum unbound valproic acid. This interaction is at times sufficient to result in clinical valproic acid toxicity.

Effect of valproic acid on the pharmacokinetics of other drugs

Addition of valproic acid has been found to increase the serum levels of phenobarbital by 57–81%. Valproic acid also markedly inhibits the elimination of lamotrigine, leading to a two- to three-fold prolongation of the lamotrigine half-life [19]. This interaction is competitive and rapidly reversible, but it seems to persist at low valproic acid concentrations and to be already maximal, in adults, at valproic acid doses of about 500 mg/day. In patients taking valproic acid, lamotrigine must be introduced at lower doses. Conversely, when discontinuing valproic acid in a patient taking lamotrigine, it is crucial to increase the dose of lamotrigine, at the latest when valproic acid is stopped altogether [20].

The serum levels of ethosuximide can also be raised by the addition of valproic acid, mostly in the presence of additional AEDs. The serum levels of carbamazepine itself are not raised by valproic acid, but the levels of its active metabolite, carbamazepine-10,11-epoxide, may double after adding valproic acid. An even greater increase in the serum levels of carbamazepine-10,11-epoxide is caused by valpromide, an amide derivative of valproic acid which acts at least in part as a valproic acid prodrug. Valproic acid may also raise the levels of rufinamide, felbamate and lorazepam, as well as those of certain tricyclic antidepressants, zidovudine and the calcium channel blocker nimodipine (Table 55.1). In contrast to enzyme-inducing AEDs, valproic acid does not affect the serum levels and the efficacy of oral contraceptives.

Valproic acid displaces phenytoin from plasma protein binding sites, and may simultaneously inhibit phenytoin metabolism. When valproic acid is added on to the therapeutic regimen of patients stabilized on phenytoin, the total phenytoin levels may show little change or even fall, whereas the unbound phenytoin concentration may be unchanged or increased. In any case, in the presence of valproic acid co-medication, the total serum levels of phenytoin underestimate the concentration of unbound, pharmacologically active drug.

Other interactions between valproic acid and other drugs are listed in Table 55.1.

Pharmacodynamic drug interactions

In addition to inhibiting lamotrigine metabolism, valproic acid may interact with lamotrigine pharmacodynamically. In fact, patients with various seizure types that failed to respond to maximally tolerated doses of either drug alone may achieve seizure control when the two agents are combined [21]. This interaction is often beneficial, but it also entails a risk of reciprocal potentiation of adverse effects, particularly tremor, and a reduction in the dosage of both drugs is usually required.

The combination of ethosuximide and valproic acid can also lead to a favourable pharmacodynamic interaction that may allow the control of absence seizures in patients not responsive to monotherapy with either drug.

Serum level monitoring

Monitoring the serum levels of valproic acid is common practice, but it is of relatively limited value [21]. One reason is that there is a considerable fluctuation in valproic acid levels over a 24-h period because of the short half-life of the drug, and the reproducibility of serum levels in a given patient has been shown to be relatively poor. Another reason is that there seems to be a poor correlation between serum valproic acid levels at a given time and clinical effect at the same time, since the pharmacodynamic effects may lag significantly behind the serum drug concentration [22]. The usually quoted reference range for serum valproic acid levels is 50–100 mg/L (350–700 μmol/L). However, levels of up to 150 mg/L may be both necessary and well tolerated in some patients. Serum valproic acid levels can be especially valuable in selected cases, particularly during combination therapy with enzyme-inducing drugs, but the result of a single measurement has limited value and needs to be interpreted cautiously.

Efficacy

Within a relatively short time after its introduction into routine clinical use, it became apparent that valproic acid is highly effective in the treatment of primarily generalized seizures, such as absence seizures, generalized tonic–clonic seizures and myoclonic seizures. Valproic acid was the first true broad-spectrum AED to become available, with good or at least some degree of efficacy

against most seizure types. The treatment of absence seizures was the primary indication of valproic acid when it was released in North America in 1978. A recent randomized study revealed that valproic acid remains the clinically most effective drug for the treatment of idiopathic generalized epilepsies or difficult to classify epilepsies [23].

Absence seizures

The ability of valproic acid to suppress or reduce spike–wave discharges when administered to patients with typical and atypical absence seizures has been reported on several occasions.

In at least two studies, the efficacy of valproic acid and ethosuximide in the treatment of absence seizures was compared and found to be equal [24,25]. A double-blind cross-over study of valproic acid and ethosuximide, in which the measure of efficacy was the frequency and duration of generalized spike–wave bursts on electroencephalogram (EEG) telemetry, was carried out in 16 patients who were not previously treated for absence seizures and 29 refractory patients [25]. In previously untreated patients, ethosuximide and valproic acid were equally effective. Valproic acid achieved seizure control much faster than lamotrigine in an open-label randomized comparison in 37 children, but the difference in overall seizure freedom at 1 year did not reach statistical significance, possibly because of the low statistical power associated with the low sample size [26].

Simple absence seizures could be completely controlled by valproic acid monotherapy in 11 out of 12 patients [27], in 10 out of 12 patients [28], in 14 out of 17 patients [29] and in 20 out of 21 patients [30], respectively. Because of the limited methodological quality or statistical power of the studies, review of the available evidence cannot demonstrate a difference in efficacy between valproic acid, lamotrigine and ethosuximide against absence seizures.

Full control of absence seizures appears more likely if these seizures occur alone than if they are mixed with another seizure type. Patients with recurrent absence status have also been treated effectively with valproic acid. Atypical or 'complex' absences are generally less responsive to valproic acid than simple absences. The combination of valproic acid with ethosuximide or with lamotrigine may be effective in suppressing absence seizures uncontrolled by any of these drugs given alone.

Generalized tonic–clonic seizures

Apart from being a first-line drug for absence seizures, valproic acid can be highly effective in the treatment of certain generalized convulsive seizures [31]. Valproic acid was used in monotherapy in 36 patients with primarily generalized tonic–clonic seizures, of whom 24 had been treated previously with other AEDs [27]. Seizures were fully controlled in 33 of these patients. Generalized tonic–clonic seizures were fully controlled by add-on valproic acid in 14 out of 42 patients with intractable seizures [32]. In 61 previously untreated patients with generalized tonic–clonic, clonic or tonic seizures, valproic acid was compared with phenytoin [33]. In 73% of these patients receiving valproic acid and in 47% of the patients treated with phenytoin, the seizures came under control during the time of observation. This response increased to 82% for valproic acid and 76% for phenytoin when seizures that occurred before therapeutic plasma drug levels had been reached were disregarded. A 2-year remission was achieved in 27 out of 37 patients with valproic acid and in 22 out of 39 patients with phenytoin in another randomized study comparing valproic acid with phenytoin in patients with previously untreated tonic–clonic seizures [34]. In two studies of patients with primary (idiopathic) generalized epilepsies, valproic acid was assessed in monotherapy. In these two studies of patients who had only generalized tonic–clonic seizures, complete seizure control was achieved in 51 out of 70 patients [35] and in 39 out of 44 patients [30]. In children with generalized tonic–clonic seizures, monotherapy with valproic acid was also found to be highly effective.

Myoclonic seizures

Valproic acid is a drug of first choice for most myoclonic seizures, particularly those occurring in patients with primary or idiopathic generalized epilepsies. Sixteen out of 23 patients with myoclonic epilepsy of adolescence experienced full seizure control with valproic acid monotherapy [27]. In addition, out of 22 patients with myoclonic epilepsy of adolescence and with an abnormal EEG response to intermittent photic stimulation, of whom 17 had failed to respond to previous medications, full seizure control was achieved in 17 patients [27]. Regardless of the associated clinical seizure type, EEG sensitivity to intermittent photic stimulation is easily suppressed by valproic acid. In a representative study, treatment with valproic acid monotherapy was assessed in a group of patients with primary generalized epilepsies; 22 patients had myoclonic seizures and 20 of those had at least one other seizure type: either absence or tonic–clonic seizures [30]. In 18 of these 22 patients, myoclonic seizures were controlled by valproic acid monotherapy.

The response to valproic acid in patients with juvenile myoclonic epilepsy is excellent, and valproic acid remains a drug of first choice for this condition in most patients, at least in terms of efficacy. There is also a good response to treatment with valproic acid in benign myoclonic epilepsy of infancy [36], which belongs to the group of the primary or idiopathic generalized epilepsies. Some success has been achieved with valproic acid in postanoxic intention myoclonus, which is usually quite refractory to treatment [37–39]. In the treatment of myoclonic and tonic–clonic seizures in patients with severe progressive myoclonus epilepsy, a combination of valproic acid and clonazepam has been advocated [40].

Infantile spasms and Lennox–Gastaut syndrome

Compared with the more benign idiopathic generalized epilepsies, available information on the use of valproic acid is much less extensive in relation to the treatment of severe generalized encephalopathic epilepsies of infancy and childhood, such as West syndrome and Lennox–Gastaut syndrome. Valproic acid is less effective in the treatment of these severe forms of generalized epilepsy, as is the case for all other antiepileptic medications. In a larger series of patients treated with valproic acid, 38 had myoclonic astatic epilepsy, a term used synonymously with Lennox–Gastaut syndrome by the authors of this study. Seven of these 38 patients became and remained seizure free with valproic acid. A 50–80% improvement was achieved after the introduction of valproic acid in an additional one-third of these patients, and other AEDs could be withdrawn or reduced. Seizures were fully

controlled in three out of six patients with myoclonic absence epilepsy in the same series, all of them on combination therapy. In a group of 100 children treated with valproic acid, seizure control was achieved in 12 out of 27 children with 'absences and other seizures' and in 9 out of 39 children with atonic seizures [16].

In the majority of publications on the use of valproic acid for the treatment of infantile spasms, the number of patients is small, or patients receiving corticotropin and valproic acid simultaneously were included. In one series of 19 infants with infantile spasms, valproic acid was used without corticotropin [41]. Eight of these 19 infants experienced good seizure control with valproic acid as their first drug, and they did not require corticotropin. The patients received valproic acid doses ranging from 20 to 60 mg/kg/day, and those who failed initial treatment with either valproic acid or corticotropin were subsequently switched to the other drug. There was a tendency towards a better response to corticotropin when the two groups were compared, but the incidence and severity of side-effects was lower with valproic acid. In a series of 18 infants with infantile spasms who were not previously treated with corticotropin, a low dose of 20 mg/kg/day of valproic acid was used [42]. The short-term results were described as good to excellent in 12 of these patients. Seven patients had residual seizure activity on follow-up, and moderate to severe mental retardation was diagnosed in 16 patients. The conclusion by the authors was that the efficacy of valproic acid was similar to the efficacy of corticotropin, and that valproic acid was associated with fewer side-effects.

Partial seizures

The efficacy of valproic acid against partial seizures was assessed systematically only after its role in the treatment of generalized seizures had been established. Some benefit of valproic acid against partial seizures was suggested by preliminary information based on subgroups of patients in studies not dealing primarily with partial seizures [16]. The first direct comparison of valproic acid with carbamazepine in the treatment of partial seizures was an open study in 31 previously untreated adults [43]. Seizure control was achieved in 11 patients on valproic acid and in eight patients on carbamazepine, but in 12 out of the 31 patients follow-up was less than 1 year. In a prospective study of 79 patients with previously untreated simple partial or complex partial seizures, comparison between carbamazepine, phenytoin and valproic acid in monotherapy revealed no difference in efficacy among the three drugs [44]. A group of 140 adults with previously untreated seizures were randomized to monotherapy with phenytoin or valproic acid [45]. In 76 patients, the seizures were tonic–clonic and in 64 they were predominantly complex partial. No difference between the two drugs in either subgroup was found in terms of 2-year remission rate or time to first seizure. A remarkable response was found in a retrospective study of valproic acid monotherapy in 30 patients with simple partial and complex partial seizures, in whom previous drugs had failed because of allergies or lack of efficacy [46]. Only eight patients were not improved, whereas seizure control was achieved in 12 patients, and a more than 50% seizure reduction occurred in 10 patients.

The most comprehensive controlled comparison between valproic acid and carbamazepine monotherapy in the treatment of partial and secondarily generalized seizures was carried out by Mattson and co-workers [47]. A total of 480 adult patients were included in this multicentre, double-blind, randomized trial, and several seizure indicators, as well as neurotoxicity and systemic toxicity, were assessed quantitatively. In the final analysis, four out of five efficacy indicators were significantly in favour of carbamazepine against complex partial seizures, and a combined composite score for efficacy and tolerability was higher for carbamazepine than for valproic acid at 12 months, but not at 24 months. For secondarily generalized seizures, outcomes did not differ between the two drugs.

In a subsequent double–blind trial designed primarily to meet regulatory requirements, a group of 143 adults with poorly controlled partial seizures was randomized to monotherapy with valproic acid (administered as divalproex sodium) at low serum levels (25–50 mg/L) or at high serum levels (80–150 mg/L). There was a significantly greater reduction in the frequency of both complex partial and secondarily generalized tonic–clonic seizures among patients in the high-level group [48].

Two studies comparing valproic acid with other AEDs were carried out in children. In the first study, carbamazepine or valproic acid was administered in a randomized fashion to a total of 260 children with newly diagnosed primary generalized or partial epilepsy, and they were then followed up for 3 years [49]. Doses were titrated as needed and as tolerated according to the clinical response. Against generalized as well as partial seizures, equal efficacy was found for the two treatments, and adverse events were mostly mild for both drugs. In the second study, 167 children with untreated tonic–clonic or partial seizures entered into a randomized, unblinded trial in which four AEDs, phenobarbital, phenytoin, carbamazepine and valproic acid, were compared [50]. At 1, 2 or 3 years, there was no difference in efficacy in terms of time to first seizure and time to 1-year remission. Unacceptable side-effects necessitating withdrawal occurred in 6 out of 10 patients on phenobarbital, which was prematurely removed from the study, in 9% of children on phenytoin and in 4% each of children taking carbamazepine or valproic acid.

A meta-analysis of trials comparing valproic acid and carbamazepine concluded that carbamazepine was more effective than valproic acid in reducing time to first seizure and time to 12 months of remission [51].

Status epilepticus

A number of studies have provided evidence that valproic acid, used mostly by the intravenous route, is a valuable agent for the treatment of both convulsive and non-convulsive status epilepticus. The use of valproic acid in the management of status is discussed in some detail in Chapter 18.

Other seizure disorders

The efficacy of valproic acid in the prevention of febrile seizures was assessed in several studies. Valproic acid was found to be as effective as phenobarbital in some studies, whereas in other studies it was more effective than phenobarbital, placebo or no treatment in terms of reducing the risk of seizure recurrence [52]. In children with a high risk of recurrence of febrile seizures, treatment with intermittent diazepam during febrile episodes was as

effective as continuous prophylaxis with valproic acid [53]. However, valproic acid cannot be recommended for the prophylaxis of febrile seizures based on risk versus benefit ratio considerations.

Seizures have also been treated with valproic acid either rectally or orally [14] in a small group of newborns. A loading dose of 20–25 mg/kg was followed by a maintenance dose of 5–10 mg/kg every 12 h [14]. Results were generally favourable. The elimination half-life of valproic acid was shown to be longer in newborns (26.4 h), and these newborns also developed higher levels of ammonia.

Non-epilepsy indications

Valproic acid is an established agent for the management of bipolar disorder, mania and migraine. Its use in these and in other indications has been reviewed [54–57].

Adverse effects

The distinction between adverse effects that are non-idiosyncratic and dose related and those that are idiosyncratic is not always easy in the case of valproic acid. Some reactions are indeed fairly predictable and dose related, such as tremor or thrombocytopenia. However, a number of adverse events that appear to be idiosyncratic because they only occur in a small fraction of patients are also more likely to occur at high doses or high serum drug levels, such as certain cases of confusion or stupor, and neural tube defects. Pancreatitis is also very rare, but its occurrence has not been found to be related to higher serum valproic acid levels. Finally, certain side-effects such as hair changes and weight gain, which are too common to be considered idiosyncratic, could never be clearly shown to be dose related. Table 55.2 summarizes the main adverse effects of valproic acid.

Table 55.2 Adverse effects of valproic acid.

Neurological
Tremor
Drowsiness
Lethargy
Confusion
Reversible dementia
Brain atrophy
Encephalopathy
Extrapyramidal symptoms
Gastrointestinal
Nausea
Vomiting
Anorexia
Gastrointestinal distress
Weight gain
Liver and pancreas
Hepatic failure
Pancreatitis
Haematological
Thrombocytopenia
Decreased platelet aggregation
Fibrinogen depletion
Other coagulation disorders
Neutropenia
Bone marrow suppression
Metabolic/endocrine
Hyperammonaemia
Hypocarnitinaemia
Hyperinsulinism
Menstrual irregularities
Polycystic ovaries
Teratogenic
Major malformations, including neural tube defects and possible developmental delay in offspring
Miscellaneous
Hair loss
Facial and limb oedema
Nocturnal enuresis
Decreased bone mineral density
Hyponatraemia
Skin rashes
Immune-mediated idiosyncratic reactions

Neurological adverse effects

Probably the most common neurological adverse effect of valproic acid is a tremor with the characteristics of an essential tremor. Valproic acid-induced tremor has been shown to be dose related and to occur in about 10% of patients. Propranolol may be effective in controlling the tremor if the symptom does not improve sufficiently following reduction of the dose.

Less common adverse effects of valproic acid are asterixis and reversible parkinsonism. Although drowsiness, lethargy and confusional states are uncommon with valproic acid, they may occur in some patients, usually at levels above 100 mg/L. In patients treated with valproic acid, well-documented cases of reversible dementia and pseudoatrophy of the brain [58] have also been reported.

A unique and rather specific adverse effect of valproic acid, characterized by acute mental changes that can progress to stupor or coma, has been well described [59]. A typical feature is usually a rather abrupt change of the EEG tracing, with generalized delta slowing. The precise mechanism of this idiosyncratic reaction is not known with certainty. Hyperammonaemia or carnitine deficiency can be associated, but do not seem to be the cause [60]. This encephalopathic state appears to be more likely to occur when valproic acid is added to another AED, or vice versa. It is usually reversible within 2–3 days upon discontinuation of valproic acid or of the other AED [61].

Valproic acid does not appear to be associated with a high overall incidence of dose-related effects on cognition or behaviour. A suggested possible psychotropic effect of valproic acid has not been confirmed in a later controlled study [62].

Gastrointestinal adverse effects, including weight gain

Nausea, vomiting, gastrointestinal distress and anorexia are the most frequent gastrointestinal adverse effects of valproic acid. They are likely to be due in part to direct gastric irritation of the gastric mucosa, and their incidence is indeed lower when patients take enteric-coated tablets.

Another quite common problem with valproic acid is excessive weight gain [63]. This is not entirely due to increased appetite, and decreased β-oxidation of fatty acids has been postulated as a possible mechanism. Obese valproic acid-treated men have been reported to have higher serum insulin levels than obese control subjects [64,65]. Rather than increased insulin secretion or insulin resistance, the mechanism for this may be interference with hepatic insulin metabolism [66]. It has also been shown that patients who developed obesity on valproic acid had increased leptin levels and decreased ghrelin and adiponectin levels [65]. Weight gain tends to be a bothersome side-effect, especially in young women, despite recommendations for diet and exercise. In children, excessive weight gain seems to be less of a problem, and one study suggested that valproic acid does not cause more weight gain than carbamazepine in children [67].

Hepatic and pancreatic toxicity

One of the most feared adverse effects of valproic acid remains fatal hepatotoxicity [12]. Patients with inborn errors of metabolism, such as urea cycle defects [68], organic acidurias and a number of other disorders [69], are at special risk for severe liver toxicity, and valproic acid should be preferably avoided in these patients. Apart from this, young age and polytherapy have been identified as the two main risk factors. The risk of fatal hepatotoxicity on polytherapy with valproic acid has been estimated at approximately 1 in 600 below the age of 3 years, 1 in 8000 from 3 to 10 years, 1 in 10 000 from 11 to 20 years, 1 in 31 000 between 21 and 40 years and 1 in 107 000 above the age of 41 years [12]. On monotherapy, the risk is much lower and has been estimated to vary between 1 in 16 000 (3–10 years old) and 1 in 230 000 (21–40 years old). For certain age groups, no fatalities have been reported. Although it is commonly done routinely, laboratory monitoring is of little value, because a benign elevation of liver enzymes is common with valproic acid, and severe hepatotoxicity is usually not preceded by a progressive elevation of liver enzymes. The most important step in the diagnosis of hepatic failure due to valproic acid is probably recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, jaundice, oedema and at times loss of seizure control. Increased production of toxic valproic acid metabolites has been considered to be a possible cause of valproic acid hepatotoxicity, but this has not been well documented [70]. There is also evidence of a protective effect of carnitine administration (especially intravenously) in cases of severe valproic acid hepatotoxicity [71]. According to a panel of experts, L-carnitine supplementation is strongly suggested in the following groups of patients: those with certain secondary carnitine deficiency syndromes, symptomatic valproic acid-associated hyperammonaemia, multiple risk factors for valproic acid hepatotoxicity or renal-associated syndromes, infants and young children taking valproic acid, patients with epilepsy using the ketogenic diet who have hypocarnitinaemia, patients receiving dialysis, and premature infants who are receiving total parenteral nutrition [72].

The development of acute haemorrhagic pancreatitis is another serious complication of valproic acid treatment [73,74]. The occurrence of vomiting and abdominal pain should raise the suspicion of this complication. The most helpful diagnostic tests are serum amylase and lipase, and abdominal ultrasound may then be considered. However, amylase may be elevated in 20% of asymptomatic patients on valproic acid [75], and pancreatitis has been described in a patient with normal amylase but elevated lipase [76].

Haematological adverse effects

Although valproic acid therapy is commonly associated with haematological alterations, these are seldom severe enough to necessitate discontinuation of the drug [77]. Thrombocytopenia is by far the most frequently diagnosed haematological side-effect [78]. It is usually dose or serum concentration dependent and tends to improve with dosage reduction. In conjunction with other valproic acid-induced disturbances of haemostasis, such as impaired platelet function, fibrinogen depletion and coagulation factor deficiencies [79,80], thrombocytopenia may cause bruising or bleeding. It is therefore generally recommended to discontinue valproic acid about 1 month before elective surgery, especially when the surgical procedure is considered to be associated with high blood losses. However, no objective evidence of excessive operative bleeding during neurosurgical procedures in patients maintained on valproic acid could be found in independent studies [81–83].

In addition to changes related to coagulation, valproic acid can also occasionally cause neutropenia and bone marrow suppression.

Metabolic, endocrine and reproductive disorders, including teratogenicity

Because hyperammonaemia is a very common finding in patients on chronic valproic acid therapy, particularly in those taking valproic acid together with an enzyme-inducing AED, and it is usually asymptomatic, routine monitoring of ammonia is not warranted [84]. It has been proposed that the origin of the excessive ammonium may be renal. It has also been shown that hyperammonaemia can be reduced by L-carnitine supplementation, but there is no documentation that this is necessary or clinically beneficial [85].

Symptomatic cases of hyperammonaemia have also been reported. In fact, ammonia levels were initially measured in symptomatic patients with changes in mental status, and the finding of elevated values was considered to be the cause of the symptoms even though this interpretation might not have been correct in all cases. Valproic acid-induced encephalopathic hyperammonaemia can be severe, and lethal cases of hyperammonaemic coma or Reye-like syndrome have been reported, particularly in patients with urea cycle disorders [85]; this can be regarded as a contraindication to the use of valproic acid.

Independently from hyperammonaemia, carnitine levels can be lowered by chronic treatment with valproic acid, especially in polytherapy [86]. One patient who developed acute encephalopathy and cerebral oedema after acute administration of valproic acid was found to have low carnitine levels, but a prominent role for carnitine deficiency in the development of severe adverse effects of valproic acid has never been established. However, in cases of acute valproic acid overdose, a beneficial role of L-carnitine supplementation has been suggested [87].

Menstrual irregularities, hormonal changes such as hyperandrogenism and hyperinsulinism [88,89], and pubertal arrest in

women have all been reported in association with valproic acid treatment. The association between valproic acid therapy and polycystic ovary syndrome has been another concern. This may include obesity, hirsutism, hyperandrogenism, anovulatory cycles and menstrual disorders. Although polycystic ovary syndrome is more common in women with epilepsy (13–25%) than in the general female population (4–6%), it has been reported to be even higher among those treated with valproic acid (up to 64%). However, it is still openly debated to what extent these observations are significant and reproducible [90–92].

When taken during pregnancy, valproic acid has been found to be associated with an increased risk of major malformations [93]. In particular, treatment with valproic acid during the first trimester of pregnancy has been reported to be associated with an estimated 1–2% risk of neural tube defects in the newborn, mostly spina bifida [94]. The risk of spina bifida and other congenital malformations appears to increase at higher doses of valproic acid. In animal studies, neural tube defects also seem to correlate with higher peak serum levels of valproic acid. A genetic susceptibility may also be involved. Folate supplementation is recommended in all women with childbearing potential treated with valproic acid, although a protective effect of folate against valproic acid-induced teratogenicity has not been established. It has been suggested more recently that exposure to valproic acid *in utero* may also result in developmental delay, including learning disability, in the offspring [95]. Risks for fetal and postnatal development in relation to exposure to valproic acid and other AEDs during pregnancy are discussed in greater detail in Chapter 25.

Miscellaneous adverse effects

Early during treatment with valproic acid, excessive hair loss or thinning of the hair may be seen. This does not represent visible alopecia, but patients or parents may see more hair on the comb or in the shower. Although the hair tends to grow back, its texture or colour may become different. In some cases, more prominent hair loss and full-blown alopecia may occur.

Although valproic acid is not an enzyme-inducing drug, it may also decrease bone mineral density, with a resulting increased risk of fractures. Unlike enzyme-inducing AEDs, valproic acid does not cause bone loss through hypovitaminosis D, and the precise mechanism has not been elucidated.

Rare adverse effects include facial or limb oedema even in the absence of hepatic injury, secondary nocturnal enuresis (especially in children), hyponatraemia [96,97], skin rashes and systemic lupus erythematosus.

Current place in therapy

Valproic acid is a broad-spectrum AED and remains a first-line therapy in idiopathic generalized epilepsies. Its efficacy in these forms of epilepsy has been confirmed by decades of clinical use and has remained unsurpassed. Valproic acid is a first-line or adjunctive therapy in cryptogenic or symptomatic generalized epilepsies. It can also be effective, but does not represent a first-line therapy, against partial seizures. In the treatment of juvenile myoclonic epilepsy, valproic acid is highly effective against all seizure types that may occur and, unlike lamotrigine, it was not found to exacerbate myoclonic seizures.

There are two populations of patients in whom valproic acid should be used with great caution: infants and female patients of childbearing age. The first group is at higher risk of potentially fatal liver toxicity, and in the latter group, teratogenicity in the form of a substantial increase in the risk of spina bifida and other major congenital malformations markedly limits the use of valproic acid.

Although many different formulations of valproic acid have been marketed, their types and availability vary from country to country. Commonly used dosage forms include immediate-release capsules, tablets and syrup, enteric-coated tablets of sodium valproate or divalproex sodium, divalproex sodium enteric-coated sprinkles, various sustained-release oral preparations, valpromide (the amide of valproic acid) tablets and a formulation of sodium valproate for intravenous use. In addition, solid-dose forms especially suitable for younger children are available, such as sprinkles consisting of capsules containing enteric-coated particles of divalproex sodium; the capsules can be opened and the contents can be sprinkled on food, or the capsules can be swallowed unopened. Another convenient formulation for paediatric use consists of sachets containing small particles (microspheres) of sustained-release valproic acid.

The initial recommended dose of valproic acid is approximately 15 mg/kg/day in children or 400–500 mg/day in adults. This can be increased subsequently, as necessary and as tolerated, by 250–500 mg/day (or 5–10 mg/kg/day in children) at appropriate intervals. The optimal dose or serum concentration may be a function of the patient's seizure type and syndromic form. In idiopathic generalized epilepsies, monotherapy with daily doses between 10 and 20 mg/kg is often sufficient for full seizure control [16]. Higher doses in milligrams per kilogram per day are often required in children. In patients who are also taking enzyme-inducing AEDs, doses of 30–60 mg/kg/day (in children even more than 100 mg/kg/day) may be necessary to achieve adequate serum valproic acid levels. When using immediate-release or enteric-coated formulations, it is common practice to divide the daily oral dose of valproic acid into two or three single doses because of the relatively short elimination half-life of the drug. However, equally good results have been achieved with a single daily dose, which may be explained by the pharmacodynamic profile of valproic acid. In fact, it appears that, at least in some cases, the maximal therapeutic effect may lag by days or weeks behind the achievement of stable doses or serum drug levels. Sustained-release formulations are generally administered twice daily or once daily, depending on the properties of the formulation and the characteristics of the patient (twice-daily dosing is generally more appropriate for patients with shorter half-lives, such as children co-medicated with enzyme-inducing AEDs).

Valproic acid can be administered intravenously if therapeutic serum drug levels are to be achieved rapidly, or in patients who are unable to take oral medication [98]. This route may also be used for the treatment of status epilepticus. The usual initial dose is 15–20 mg/kg administered over 5–10 min (at a rate of 1.5–3.0 mg/kg/min), followed by constant infusion at a rate of 0.5 mg/kg/h (1 mg/kg/h for patients on enzyme-inducing AEDs) in adults

and 1.0 mg/kg/h (1.5 mg/kg/h for patients on enzyme-inducing AEDs) in children. However, more rapid administration (up to 6 mg/kg/min) of loading doses (up to 45 mg/kg) has been tolerated well [99]. A subsequent administration should be given within 6 h in those receiving intravenous replacement therapy or bolus dosing, because of the rapid fall in serum drug levels and the possible re-emergence of seizures.

When chronic valproic acid therapy is initiated, it is common practice to routinely monitor liver enzymes and complete blood counts with platelets, starting at baseline, then 1–3 months after initiation, and about every 6 months after this if the results are normal. Haematological abnormalities are likely to be discovered. However, severe hepatotoxicity is unlikely to be detected by routine monitoring of liver enzymes, because of its rapid onset and progression. Serum ammonia should be determined, especially in the presence of mental status changes. If gastrointestinal symptoms occur, especially vomiting and abdominal pain, amylase and lipase should be checked, in addition to liver function tests.

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56 Vigabatrin

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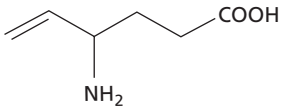

Primary indications	Monotherapy of infantile spasms (West syndrome). May also be of value as adjunctive therapy for partial and secondary generalized seizures refractory to other drugs
Usual preparations	Tablets: 500 mg; powder (sachets): 500 mg
Usual dosages	75–150 mg/kg/day (infantile spasms). For partial seizures, maintenance dosages are generally in the range of 1000–3000 mg/day (adults), 500–1000 mg/day (children weighing 10–15 kg), 1000–1500 mg/day (children weighing 15–30 kg) and 1500–3000 mg/day (children weighing over 30 kg). In partial seizures, treatment should be initiated at a low dosage (e.g. 500 or 1000 mg/day in adults) and increased gradually
Dosing frequency	Twice daily
Significant drug interactions	Vigabatrin may reduce serum phenytoin levels
Serum level monitoring	Not useful, except for monitoring compliance
Reference range	Not applicable
Common/important adverse effects	Irreversible visual field constriction, weight gain, sedation, fatigue, dizziness, blurred or double vision, nystagmus, ataxia, paraesthesiae, amnesia, depression, psychosis, aggression, confusion, stupor. Drowsiness, insomnia, hyperactivity, agitation, hypotonia, hypertonia, aggravation of myoclonic seizures and other generalized seizure types, and gastrointestinal symptoms are seen particularly in children
Main advantages	Highly effective and relatively well tolerated in the treatment of infantile spasms
Main disadvantages	Visual field constriction, weight gain and central nervous system side-effects
Mechanisms of action	Irreversible inhibition of GABA transaminase
Oral bioavailability	≥50% for the active *S*-(+)-enantiomer
Time to peak levels	0.5–2 h
Elimination	Primarily by renal excretion in unchanged form
Volume of distribution	0.8 L/kg [1.2 L/kg for the *S*-(+)-enantiomer]
Elimination half-life	4–7 h
Plasma clearance	0.10–0.144 L/kg/h for the active *S*-(+)-enantiomer, assuming complete bioavailability
Protein binding	None
Active metabolites	None
Comment	A first-line drug for the treatment of infantile spasms, particularly those caused by tuberous sclerosis complex. Because of the risk of irreversible visual field constriction, vigabatrin is rarely used in other indications

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Introduction

Vigabatrin represents one of the few antiepileptic drugs (AEDs) that emerged from a mechanism-driven discovery strategy. Based on the evidence that γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the mammalian brain, and that epileptic seizures may result from an imbalance between excitatory and inhibitory transmission, vigabatrin was discovered through a systematic search for agents that can increase brain GABA levels by inhibiting GABA transaminase, the main enzyme responsible for the degradation of GABA [1]. Vigabatrin was initially licensed for the treatment of refractory partial-onset seizures. However, after the discovery of serious retinal toxicity, its use is currently restricted primarily to the treatment of infantile spasms.

Chemistry

Vigabatrin is a white to off-white crystalline amino acid which is highly water soluble and only slightly soluble in ethanol and methanol. Its molecular weight is 129.16, and the conversion factor from mg/L to μmoL/L is 7.75 (1 mg/L = 7.75 μmol/L). Vigabatrin exists as a racemic mixture of *S*-(+)- and *R*-(–)-enantiomers in equal proportions. Only the *S*-(+)-enantiomer is pharmacologically active [2].

Vigabatrin is available only in oral formulations (tablets and sachets, containing 500 mg each).

Pharmacology and toxicology data

Activity in experimental models of seizures and epilepsy

The anticonvulsant effects of vigabatrin have been studied in numerous animal models. The onset of anticonvulsant activity in classical models (such as the maximal electroshock test) occurs with a delay of many hours, being correlated with the slowly developing increase in GABA levels in nerve terminals rather than with the concentration of the drug in plasma [3]. Vigabatrin shows protective activity against bicuculline-induced myoclonic seizures, strychnine-induced tonic seizures, isoniazid-induced generalized seizures, audiogenic seizures in mice, light-induced seizures in baboons and amygdala-kindled seizures in rats [4].

Animal toxicology data

Standard preclinical safety studies in rats, mice, dogs and monkeys demonstrated no significant adverse effects of vigabatrin on the liver, kidney, lung, heart or gastrointestinal tract. Vigabatrin is also devoid of mutagenic or carcinogenic effects. However, in the brain, microvacuolation was observed in white matter tracts of rats, mice and dogs at doses of 30–50 mg/kg/day. In the monkey, these lesions were minimal or equivocal. Microvacuolation is caused by a separation of the outer lamellar sheath of myelinated fibres, a change characteristic of intramyelinic oedema. In both rats and dogs, intramyelinic oedema was reversible upon discontinuation of the drug, and even with continued treatment histological regression was observed. In rodents, minor residual changes consisting of swollen axons and mineralized microbodies were observed [5,6].

Vigabatrin-associated retinotoxicity has been observed in albino rats, but not in pigmented rats, dogs or monkeys. Retinal changes in albino rats were characterized as focal or multifocal disorganization of the outer nuclear layer with displacement of nuclei into the rod and cone area. The other layers of the retina were not affected. Although the histological appearance of these lesions was similar to that found in albino rats following excessive exposure to light, the retinal changes may also represent a direct drug-induced effect [5].

Mechanism of action

Vigabatrin is an irreversible suicide inhibitor of GABA transaminase, the enzyme responsible for the transamination of GABA to form succinic acid semialdehyde. Vigabatrin itself is a substrate of GABA transaminase. The mechanism of enzyme inhibition involves the binding of the drug to GABA transaminase, which selectively converts it to a reactive intermediate. The intermediate, in turn, binds covalently to the enzyme, causing its irreversible inactivation [1,7].

Inhibition of GABA transaminase results in reduced catabolism of GABA and prolonged elevation of brain GABA levels, without any major influence on other enzymes involved in GABA synthesis and metabolism. The effect of vigabatrin is maximal 3–4 h after administration, and is maintained for at least 24 h. In fact, the duration of pharmacological effect is determined not by the half-life of the drug, but by the ability of the body to resynthesize GABA transaminase. Restoration of normal enzyme activity after withdrawal of vigabatrin takes several days [8]. Vigabatrin also significantly reduces the activity of plasma alanine aminotransferase by 20–100% [9].

In patients with epilepsy, a dose-related (up to a dose of 3 g/day) elevation in the levels of free GABA, total GABA and homocarnosine (a dipeptide of GABA) in the cerebrospinal fluid (CSF) has been demonstrated [10]. ^{1}H-MR spectroscopy has also shown that the brain GABA content in the occipital region of patients with epilepsy increases two- to threefold [11,12]. Increasing vigabatrin dosage from 3 to 6 g/day did not result in a further increase in brain GABA concentrations, most probably because of feedback inhibition of glutamic acid decarboxylase, the GABA-synthesizing enzyme, at high GABA concentrations.

Pharmacokinetics

Pharmacokinetics in adults

Vigabatrin shows linear pharmacokinetics over the dose range of 0.5–4 g. The drug is rapidly absorbed from the gastrointestinal tract and peak serum concentrations are reached within 0.5–2 h after oral intake [13]. Based on the recovery of unchanged drug in urine, the oral bioavailability has been estimated at ≥50% for the active *S*-(+)-enantiomer and at ≥65% for the inactive *R*-(–)-enantiomer [13]. After a single dose, peak serum concentrations of the *S*-(+)-enantiomer are about one-half those of the *R*-(+)-enantiomer, whereas areas under the serum concentration–time curve (AUC) are about 25% lower for the *S*-(+)- than for the *R*-(–)-enantiomer [13]. Food does not influence vigabatrin absorption [14].

Vigabatrin is widely distributed in the body and is not bound to plasma proteins, The volume of distribution calculated from the serum concentrations of racemic drug is about 0.8 L/kg, but it appears to be higher (about 1.2 L/kg) for the S-(+)-enantiomer [15]. Vigabatrin levels in the CSF are approximately 10% of those in the blood [16]. The passage of both vigabatrin enantiomers across the human placenta is slow, and the breast milk to plasma concentration ratio for the active S-enantiomer is below 0.5 [17].

The elimination of vigabatrin is primarily through the kidney in unchanged form. The elimination half-life is between 5 and 7 h for both enantiomers but slightly shorter half-life values of 4–6 h have been reported in patients taking enzyme-inducing AEDs [18].

Because the clearance of *R*-(–)- and *S*-(+)-vigabatrin is highly correlated with creatinine clearance, a reduction in glomerular filtration rate, as observed physiologically in old age, is associated with a decrease in the clearance of both vigabatrin enantiomers [19].

Pharmacokinetics in infants and children

Mean values of peak serum concentration (C_{max}) and AUC values of the active *S*-enantiomer of vigabatrin were significantly lower for the active *S*-(+)-enantiomer than for the *R*-(–)-enantiomer following single oral doses of 125 mg racemic vigabatrin in six neonates, whereas no difference between the two enantiomers was found in time to reach peak plasma concentrations. Repeated administration of 125 mg twice daily over 4 days did not result in accumulation of either enantiomer [20].

Rey *et al*. [21] used an enantioselective assay to investigate the pharmacokinetics of vigabatrin after a single 50 mg/kg oral dose in six infants (age 5–24 months) and six children (age 4–14 years) with intractable epilepsy. AUC values of both enantiomers were lower in infants than in children, the difference being particularly marked for the *R*-(–)-enantiomer. For each enantiomer, AUC values were also lower than those reported for adult historical controls. Since the renal clearances of both enantiomers were comparable to those reported for adults, the suggestion was made that the lower AUC in infants and children could be related to a reduced oral bioavailability [15,21].

While there are data on the effect of vigabatrin on brain GABA levels measured by magnetic resonance spectroscopy in adults [22], no such data are available for children. One study used [^{11}C]flumazenil-positron emission tomography (PET) imaging in 15 children (aged 1–8 years) with pharmacoresistant epilepsy to determine whether prolonged vigabatrin treatment interferes with age-related changes in $GABA_A$ receptor binding *in vivo* [23]. Seven of these children were treated with vigabatrin (1000–2500 mg/day) for at least 3 months in addition to another AED, while eight age-matched controls were treated with one to three AEDs known not to act directly on the GABAergic system. Vigabatrin-treated children showed a significantly lower hemispheric flumazenil volume of distribution in all cortical regions and the cerebellum. It is assumed that vigabatrin induces a decrease in $GABA_A$ receptor binding in the cortex and cerebellum of the developing epileptic brain.

Pharmacokinetics in disease states

In patients with renal disease, the clearance of both vigabatrin enantiomers is reduced in proportion to the degree of renal impairment, as assessed by measuring the creatinine clearance [19]. As a result, dosage needs to be adjusted accordingly. Bachmann *et al*. [24] reported a patient with severe renal failure (creatinine clearance <5 mL/min) in whom the half-life of vigabatrin was as long as 41 h. His seizures were controlled with only 500 mg vigabatrin every 3 days. Since about 60% of the drug was removed from the blood during haemodialysis, it was recommended that in these patients the vigabatrin dose should be administered after the dialysis.

Drug interactions

Plasma vigabatrin levels [25] are not affected by concomitant intake of established AEDs [25,26], although a slightly shorter vigabatrin half-life has been reported in patients on enzyme-inducing AEDs [18]. Felbamate leads to a slight increase in the levels of the active *S*-(+)-enantiomer of vigabatrin [27].

After a latency of some weeks, vigabatrin reduces serum phenytoin levels by about 25% on average, without altering phenytoin absorption [28] or plasma protein binding [29]. The mechanism of this interaction is unclear. In children with epilepsy, the fall in phenytoin levels can be even more pronounced [30]. The serum levels of phenobarbital and primidone can also be slightly reduced by vigabatrin [18].

Vigabatrin has no effect on the plasma concentrations of valproic acid [25] and felbamate [27]. Serum carbamazepine levels are usually unaffected by vigabatrin, even though there are isolated reports of changes in carbamazepine levels in either direction [31,32].

Vigabatrin has no effect on the pharmacokinetics of oral steroid contraceptives [33].

Serum level monitoring

Since vigabatrin has an irreversible mode of action, the time-course of serum vigabatrin concentrations is dissociated from the time-course of its pharmacological effect. In a study of 16 children with refractory epilepsy, there was no strong correlation between vigabatrin dosages, plasma concentrations and clinical efficacy [34]. A poor relationship between serum vigabatrin concentrations and clinical effects has also been found in other studies, and there seems to be no indication for monitoring serum vigabatrin levels, except for a check for compliance [35].

Efficacy

Infantile spasms (West syndrome)

Infantile spasms, currently the primary indication of vigabatrin, are associated with a variety of neuropathological conditions. About 70% of spasms are symptomatic, with brain malformations and tuberous sclerosis complex accounting for up to 35% of the cases [36]. Adrenocorticotropic hormone (ACTH) or corticosteroids have been, for decades, the gold standard treatment for infantile spasms. In 1990, vigabatrin was also found to be effective against infantile spasms, and in many countries it is now regarded as a first-line drug in this condition due to its rapid onset of efficacy (mostly within 2 weeks) and its negligible adverse

effects during the acute treatment period compared with steroids. The level of evidence provided by the studies that investigated the efficacy of vigabatrin against infantile spasms has been assessed by Mackay *et al.* [37].

Class I evidence

The only study that met criteria for class I evidence was a prospective, randomized, placebo-controlled trial that enrolled 40 children with newly diagnosed infantile spasms, 20 in each cohort [38]. At the end of a 5-day double-blind phase, seven (35%) vigabatrin-treated children were spasm free and five (25%) had a resolution of hypsarrhythmia, compared with two (10%) and one (5%) respectively in the placebo group ($P = 0.063$). Relapse occurred in four (20%) of the vigabatrin-treated patients. At the end of the study, 42% of the 36 patients who entered a 24-week open-label phase were spasm free on vigabatrin monotherapy. No patient withdrew from the study because of adverse effects.

Class III evidence

Three randomized controlled studies have been reported that met the inclusion criteria of documented presence of infantile spasms and hypsarrhythmia.

Vigevano and Cilio [39] compared the efficacy of vigabatrin (100–150 mg/kg/day) and ACTH (10 IU/day) as first-line therapy in 42 infants. Using a cross-over design, the alternative drug was administered to infants who did not respond within 20 days or were intolerant to the initial therapy. Cessation of spasms was observed in 48% (11/23) of infants in the vigabatrin group, with a slightly higher efficacy in cryptogenic than in symptomatic cases (57% versus 44%), and in 74% (14/19) of infants in the ACTH group. The response to vigabatrin occurred within 14 days, and follow-up data for up to 44 months identified only one case of relapse of spasms. In the ACTH group, six patients had a relapse 40–45 days after termination of ACTH and replacement with a benzodiazepine.

A multicentre study randomly assigned 142 infants to low-dose (18–36 mg/kg/day) or high-dose (100–150 mg/kg/day) vigabatrin treatment [40]. Within 2 weeks, 23% of the infants showed complete cessation of spasms and hypsarrhythmia. This response increased to 65% at the end of the 3-month open-label period. A marked difference in clinical and electroencephalographic response in relation to dose was observed. Within the first 2 weeks, 8 of 75 (10.6%) patients in the low-dose group and 24 of 67 (35.8%) in the high-dose group responded. The response rate continued to increase during the follow-up period (42% at 4 weeks, 55% at 2 months and 65% at 3 months) at a median dosage at the time of response of 106 mg/kg (mean 95 mg/kg, range 16.9–199 mg/kg/day). Time to response was shorter in infants allocated to the high-dose regimen and in those with spasms secondary to tuberous sclerosis complex. Of the 87 patients who initially responded to vigabatrin, 14 (16%) relapsed within 3 months during continued therapy.

The third class III evidence trial, the United Kingdom Infantile Spasms Study (UKISS), was a multicentre randomized controlled trial that compared the efficacy of vigabatrin with that of prednisolone or tetracosactide [41]. Of 52 infants randomized to vigabatrin (100–150 mg/kg/day), 28 (54%) were spasm free within 2 weeks. The short-term efficacy of vigabatrin was lower than that of hormonal treatment. In fact, 70% (21 of 30) of infants who received prednisolone (10 mg four times a day for 2 weeks, increasing to 20 mg three times a day after 1 week if spasms continued) and 76% (19 of 25) of those who received tetracosactide showed cessation of spasms within the same time period. Of the 55 infants allocated to hormonal therapy, 27 were treated with vigabatrin after day 14 because of failure to achieve cessation of spasms ($n = 12$), seizure relapse ($n = 14$) or appearance of focal seizures ($n = 1$). In the group initially allocated to vigabatrin, 22 infants were switched to hormonal treatment. Adverse events were reported in 54% (28 of 52) of the infants on vigabatrin (mainly drowsiness and gastrointestinal symptoms) and in 55% (30 of 55) of the infants on hormonal therapy (mainly high blood pressure, irritability and gastrointestinal symptoms). No deaths were recorded. Response to treatment was not influenced by underlying cause, but infants with tuberous sclerosis complex were excluded from this study. At the clinical reassessment at 12–14 months of age [42], freedom from spasms was similar in each treatment group (vigabatrin 76%, hormonal treatment 75%). Five children died during the follow-up period, one due to *Staphylococcus aureus* septicaemia on day 15 of prednisolone treatment, and four children due to their underlying disease.

Relapse rates in vigabatrin-treated infants in these randomized controlled trials ranged between 8% and 20%. Except for the low-dose versus high-dose trial [40], the primary efficacy endpoint was the cessation of spasms as determined by caregiver's observations and the initial dose varied between 50 and 100 mg/kg/day, followed by titration up to 150 mg/kg/day.

Class IV evidence

A retrospective survey of 192 patients from 59 European centres analysed the safety and efficacy of vigabatrin monotherapy in newly diagnosed infantile spasms [43]. Vigabatrin dosage varied between 20 and 400 mg/kg/day (mean dose 99 mg/kg/day) and duration of therapy ranged from 2 weeks to 28.6 months. Complete cessation of spasms was observed in 68% of patients (131 of 192), 19% had a reduction in cluster frequency, 12.5% did not improve and one infant deteriorated. Concerning subgroups of aetiologies leading to infantile spasms, patients with tuberous sclerosis complex showed a very high responder rate of 97% (27 of 28), followed by infants with cryptogenic spasms (69.4%) and symptomatic spasms due to other causes (59.7%). Infants aged less than 3 months at spasm onset responded better (90%, 18 of 20) than those with later onset (65%). Relapses occurred in 21% (28 of 131 initial responders) within a mean period of 4 months. Reported adverse events were generally mild (somnolence, insomnia, hypotonia, hyperkinesias) and drug withdrawal was required in very few patients (~1%).

In addition to the studies summarized above, there have been many other reports dealing with vigabatrin therapy in newly diagnosed or drug-refractory infantile spasms. In six open-label, uncontrolled, prospective studies [44–49], clinical responses (efficacy on hypsarrhythmia was not explicitly mentioned in all studies) varied between 50% and 100% in cryptogenic cases, and between 19% and 57% in those with symptomatic infantile spasms. Relapse rates after initial successful vigabatrin therapy were low, ranging from single cases to a maximum of 14%.

Efficacy in terms of complete cessation of spasms did not differ between newly diagnosed infants (43%, 45%) [44,45] and infants who were initially drug refractory (43%, 48%) [46,50].

Response to vigabatrin occurs relatively rapidly. In all studies and reports, the time between initiation of therapy and cessation of spasms ranged from 2 to a maximum of 35 days. Sometimes response was observed after one or two doses [51]. A 2-week cut-off for qualifying responders was proposed in different controlled and open-label studies [39,40,44,47].

In the prospective studies cited above, vigabatrin was used at doses ranging from 18 to 200 mg/kg/day. Mitchell and Shah [51] suggested that response may be dose independent. They observed complete disappearance of spasms and hypsarrhythmia at doses ranging from 25 to 135 mg/kg/day in 12 of 20 infants. In contrast, an Asian study [52] mentioned a relapse rate of 56% within 6 months in initial responders, which was ascribed to an insufficient dose because those who relapsed were on a lower average dosage of 59 mg/kg/day at the time of relapse and responded to a stepped-up dose of 83 mg/kg/day. The authors suggested that at least 70 mg/kg/day is necessary to achieve adequate seizure control.

Because the occurrence of vigabatrin-induced visual field constriction seems to correlate with the duration of treatment and with the total cumulative dose [53], the question arises of how long patients with infantile spasms should be treated. A maximum treatment duration of 6 months was proposed by Capovilla *et al*. [54]. In their study, successful drug therapy was stopped after 3–6 months (mean 5.1 months) in cryptogenic as well as symptomatic cases without relapse during a follow-up period of 13–50 months. On the other hand, Kröll-Seger *et al*. [55] reported severe relapse of infantile spasms in four children with focal cortical dysplasia (and tuberous sclerosis complex in one of them), who had been treated successfully with vigabatrin for 1–5 years [55]. In these children, vigabatrin withdrawal led to recurrence of spasms refractory to vigabatrin, and to severe mental deterioration in two cases.

Efficacy in relation to aetiology: infantile spasms due to tuberous sclerosis complex

Vigabatrin has been shown to be most effective in the treatment of infantile spasms due to tuberous sclerosis complex. This observation was first made by Chiron *et al*. [50] in the early 1990s and confirmed in a subsequent multicentre retrospective survey [43]. Of 28 children with infantile spasms due to tuberous sclerosis complex, 27 showed complete cessation of spasms, which corresponds to a response rate of 96%.

These results were confirmed in a prospective randomized trial performed by Chiron *et al*. [56] that compared vigabatrin and hydrocortisone with an optional cross-over for non-responders. The study included 22 children with infantile spasms and a confirmed diagnosis of tuberous sclerosis complex. The difference in clinical and electroencephalographic response between the two treatments was highly significant. In patients randomized to vigabatrin (150 mg/kg/day), efficacy in terms of cessation of spasms was 100% (11/11), while less than one-half (5/11) of patients randomized to hydrocortisone responded. All seven patients who crossed over from hydrocortisone to vigabatrin (six for inefficacy, one for adverse events) became seizure free. The mean time to reach seizure cessation was 3.5 days for vigabatrin compared with 13 days for hydrocortisone.

In 1999, Hancock and Osborne [57] reviewed 16 studies published in the English literature on the use of vigabatrin in the treatment of infantile spasms. Out of 390 patients, 77 had been diagnosed as having tuberous sclerosis complex, while 313 has spasms due to other aetiologies or classified as idiopathic or cryptogenic. Responder rates were 95% (73/77) in patients with tuberous sclerosis complex compared with 54% (169/313) in the remaining patients. Response was observed within 1 week in the majority of patients. Cessation of the spasms seems to be associated with a marked improvement in behaviour and mental development [58].

Epileptogenesis in tuberous sclerosis complex may be caused by an imbalance of decreased inhibition secondary to molecular changes in GABA receptors in giant cells and dysplastic neurones, and increased excitation secondary to molecular changes in glutamate receptors in dysplastic neurones [59,60]. A deficiency of GABAergic interneurones may explain the early onset and severity of seizures in tuberous sclerosis complex. The particular efficacy of vigabatrin in this condition suggests that epileptogenesis caused by tuberous sclerosis complex may be related to impairment of GABAergic transmission. However, the exact mechanisms underlying the preferential response of these patients to vigabatrin are still unknown.

Riikonen [61], who considers steroids as the first-choice agents in infantile spasms due to other aetiologies, recommends vigabatrin as first choice for infantile spasms caused by tuberous sclerosis complex. Recent expert opinions in the USA also consider vigabatrin as the treatment of choice for infantile spasms secondary to tuberous sclerosis complex, and regard it as a second-line treatment for infantile spasms secondary to other aetiologies [62].

Efficacy in relation to aetiology: infantile spasms due to other aetiologies

Focal cortical dysplasia is one of the causes of infantile spasms. However, the sensitivity of magnetic resonance imaging (MRI) in diagnosing focal cortical dysplasia in infants is low, and one-third of patients with histopathologically confirmed Taylor-type focal cortical dysplasia have unrevealing MRI images [63]. Therefore, focal cortical dysplasia can be a cause for apparently 'cryptogenic' infantile spasms. Affected patients mostly present with early partial seizures with or without infantile spasms. Lortie *et al*. [64] reported on 11 children with focal cortical dysplasia who presented with early partial seizures and infantile spasms and were easily controlled with vigabatrin or ACTH. Focal seizures remained medically refractory except for one patient. However, no patient treated with vigabatrin for focal epilepsy developed infantile spasms. According to Parisi *et al*. [65], in focal cortical dysplasia vigabatrin treatment 'seems to be able to prevent diffusion of the paroxysmal activity outside of the dysplasia. Cytoarchitectural, molecular, and immunological similarities could explain the positive response of vigabatrin therapy in infants with epileptic spasms due to focal cortical dysplasia or tuberous sclerosis complex.'

A prospective study in five children with infantile spasms associated with trisomy 21 (Down syndrome) reported an immediate

response to vigabatrin in four cases [66]. These patients showed no relapse of spasms or other seizure types when vigabatrin was discontinued after 6 months of treatment.

In a patient with infantile spasms related to succinic semialdehyde dehydrogenase deficiency, a rare autosomal recessive metabolic disorder in GABA catabolism, vigabatrin was effective at the very low dose of 25 mg/kg/day [67]. There is also anecdotal evidence of a favourable response in infantile spasms associated with Aicardi's syndrome [68]. In infantile spasms related to non-ketotic hyperglycinaemia, a rare inborn error of glycine metabolism, high GABA levels produced by vigabatrin can aggravate the epileptic encephalopathy [69].

Partial-onset seizures

Adults

Studies with vigabatrin in adults have included more than 2000 patients, the majority of whom had partial seizures. After initial open and single-blind dose-finding studies, several randomized, double-blind, placebo-controlled adjunctive therapy cross-over studies in adults with refractory partial epilepsies have been completed [1,70]. A review of the first six double-blind studies demonstrated a clear response at dosages of 2 and 3 g/day [71]. Only a limited number of patients appeared to benefit from increasing dosage from 2 to 3 g/day [71], as also shown by a subsequent cross-over study from Australia. The latter study, conducted in 97 patients with uncontrolled partial seizures, compared 2 g/day with 3 g/day and showed a similar efficacy, with 42% of patients experiencing a 50% or greater reduction of seizure frequency in comparison with placebo. In addition, the number of seizure-free days was significantly higher and the duration of seizure-free periods was significantly longer during vigabatrin treatment, and more patients had less severe and shorter seizures [72].

In addition to the cross-over studies, several double-blind, placebo-controlled adjunctive therapy parallel-group studies have been carried out. The therapeutic efficacy of vigabatrin, as assessed by the percentage of patients with at least a 50% reduction in seizure frequency, was quite similar across the studies, with about 40% of patients being responders [1,70]. In the first of two studies from the USA, 92 patients received vigabatrin 3 g/day and 90 patients received placebo [73]. Significantly more patients randomized to vigabatrin were responders in terms of 50–99% reduction in seizure frequency (37% versus 18%) or seizure freedom (6% versus 1%). The second study from the USA examined three different doses (1, 3 or 6 g/day) in a total of 174 patients [74]. Only 7% of patients in the placebo group were responders, whereas responder rates at 1, 3 and 6 g/day were 24%, 51% and 54%, respectively.

A double-blind, double-dummy substitution trial compared add-on vigabatrin (2–4 g/day) and valproic acid (1–2 g/day) in carbamazepine-resistant partial epilepsy, allowing withdrawal of carbamazepine in responders. The two groups showed similar percentages of responders (53% versus 51%) and similar proportions of patients maintained on alternative monotherapy (27% versus 31%) [75].

Vigabatrin monotherapy in partial epilepsy was assessed initially in two open-label, single-centre randomized studies in 100 [76] and 51 patients [77] respectively, using carbamazepine as a comparator. Both studies failed to show statistically significant differences in efficacy, although in at least one of the studies there was a clear trend for seizure freedom rates to be greater on carbamazepine [76]. A subsequent large randomized, double-blind, parallel-group study also compared the efficacy of vigabatrin and carbamazepine monotherapy in newly diagnosed partial epilepsy. In this study, 53% of 229 patients on 2 g vigabatrin daily and 57% of 230 patients on 600 mg carbamazepine daily achieved 6-month remission. However, significantly more patients on vigabatrin withdrew due to lack of efficacy than with carbamazepine, and time to first seizure after the first 6 weeks from randomization also showed carbamazepine to be more effective. It was concluded that vigabatrin cannot be recommended as a first-line treatment for newly diagnosed partial epilepsies [78].

In another randomized trial conducted in a total of 215 patients (age range, 12–76 years), initial open-label monotherapy with carbamazepine was followed in non-responders by adjunctive treatment with either vigabatrin (1–4 g/day) or valproic acid (0.5–2 g/day). Carbamazepine could then be withdrawn and monotherapy with vigabatrin or valproic acid maintained for the final study phase. In this trial, the efficacy of the two study drugs was found to be similar [79].

Several open-label studies have assessed long-term efficacy. One commonly used indicator of long-term response is the proportion of patients remaining on treatment over time. In several long-term studies, between 39% and 72% of patients remained on vigabatrin for more than 3 years. Among the patients electing to continue treatment, the majority maintained their initial positive response, and in this particular subset (for which clearly there is a selection bias) there was no evidence of tolerance developing [80,81]. Some studies, however, did suggest that a fraction of patients may shift from responder to non-responder status over time, as also observed with other AEDs [82].

In most double-blind adjunctive therapy trials in adults with partial seizures, the daily dose of vigabatrin has been in the range of 2–3 g. Some studies, however, suggested that 1 g/day may also have some therapeutic efficacy, while there are patients who benefit from doses of 4 g/day or more. In the US study that compared daily doses of 1, 3 and 6 g, no improvement in efficacy was observed in patients randomized to 6 g compared with those randomized to 3 g, but adverse effects increased substantially at the highest dose [74]. Although vigabatrin is usually administered twice daily, a double-blind pilot study in 50 patients comparing once-daily with twice-daily dosing as adjunctive therapy found no statistically significant differences in seizure control [83].

Children

An open-label prospective study (class III evidence) in 175 children of all age groups (neonates, children and adolescents) suffering from partial-onset seizures assessed the response to vigabatrin given as add-on to carbamazepine, phenytoin or benzodiazepines. Thirty per cent of the children became seizure free, and a >50% reduction in seizure frequency was achieved in 70%. The highest percentage of responders (85%) was reported in children diagnosed with tuberous sclerosis complex, and the

lowest (45%) in those with underlying tumour aetiology [84]. A large series of open-label paediatric trials [85–94] also reported a reduction of at least 50% in seizure frequency in 23–70% of the patients. Efficacy in these studies was comparable to that reported in adults.

A randomized placebo-controlled withdrawal study (class II evidence) investigated 28 children (aged 1.5–18.5 years) with refractory partial seizures and/or other seizure types who had responded to vigabatrin as adjunctive therapy [95]. In one group, vigabatrin was stopped blindly in 3 weeks and substituted with placebo for 2 months, while the other group continued to take vigabatrin. Patients were required to exit the study if a >50% increase in seizure frequency occurred. The proportion of patients remaining in the study (primary efficacy endpoint) was greater in the vigabatrin group (93%) than in the placebo group (46%) ($P < 0.01$) and seizure frequency (secondary endpoint) was lower on vigabatrin than on placebo ($P < 0.05$).

The results obtained in children with drug-refractory partial-onset seizures prompted several investigators to use vigabatrin as a first-line drug. Three open-label studies (class III evidence), with follow-up periods of 6 months [96] or 2 years [97,98], compared vigabatrin ($n = 104$ in total) and carbamazepine ($n = 100$) monotherapy in the treatment of patients with newly diagnosed partial seizures, including idiopathic, cryptogenic and symptomatic cases. In two of the studies, allocation to treatment was randomized [96,97]. In all three trials, the efficacy of vigabatrin and carbamazepine did not reveal significant differences, and there was a suggestion for a better tolerability profile of vigabatrin during the 2-year follow-up [97]. Interictal EEG abnormalities decreased more often in children treated with vigabatrin than in those treated with carbamazepine. These studies have limitations because of their small sample size and lack of blinding, but they do provide suggestive evidence that vigabatrin monotherapy can be effective in controlling partial-onset seizures in children.

Long-term outcome data in children have been investigated in a number of adjunctive therapy studies. A 10-year follow-up study based on a retrospective chart audit [99] compared treatment outcomes in children with different types of refractory epilepsies who had been treated with lamotrigine ($n = 132$), vigabatrin ($n = 80$) and gabapentin ($n = 39$) as add-on therapy. Most of the children (46/80) had partial epilepsies. At the end of follow-up, 33% of the children on lamotrigine showed a sustained improvement in seizure frequency, compared with 19% of children who had received vigabatrin and 15% of children who had received gabapentin. However, no significant differences in efficacy among treatment groups were found in children with partial seizures. Another long-term study compared outcomes in 56 children with difficult-to-treat epilepsies who had received vigabatrin ($n = 56$) or lamotrigine [100]. Most of the patients on vigabatrin had partial epilepsies (39/56, with 11 having unclassified epilepsy), whereas the proportion of lamotrigine-treated patients with partial epilepsy was lower (23/39). Retention rate after 5 years was higher with lamotrigine than with vigabatrin (26% versus 9%). No loss of initially observed efficacy was apparent in the lamotrigine group. Conversely, 10 of the 18 initial responders in the vigabatrin group appeared to lose their response, usually within the first 9 months.

Generalized epilepsies

Some of the studies in patients with refractory partial seizures, particularly those conducted in children, also included patients with drug-resistant generalized epilepsies. One of the first multicentre open-label studies (class IV evidence), reported by Livingston *et al*. [101], investigated the outcome of add-on therapy with vigabatrin in 135 children (age range, 2 months to 12 years), of whom 42% had partial epilepsies, 29% generalized epilepsies, 19% Lennox–Gastaut syndrome and 10% West syndrome. Efficacy was better in children with partial seizures than in those with generalized seizure types. Two other paediatric studies [86,94] found vigabatrin more efficacious against partial seizures, and one [86] reported that non-progressive myoclonic epilepsy tended to be aggravated. Additionally, symptomatic generalized epilepsies tend to be more frequently associated with loss of response to vigabatrin during long-term treatment [99,102].

Similar results have been reported in other studies. In the study by Dulac *et al*. [88], response rates were highest in cryptogenic and symptomatic partial epilepsies, while symptomatic generalized epilepsies responded less favourably, Lennox–Gastaut syndrome even less favourably and three of nine patients with myoclonic epilepsy showed an increase in seizure frequency. In a retrospective study of children who had received vigabatrin or lamotrigine treatment, primary generalized tonic–clonic seizures were reported to be more frequently improved and less frequently worsened with lamotrigine than with vigabatrin, whereas for tonic seizures outcome appeared to be more favourable with vigabatrin [93]. Conversely, no significant differences in clinical response between partial-onset and generalized seizure types were reported in a few open-label paediatric studies [91,92,103,104]. The study by Gherpelli *et al*. [103], which excluded from analysis children with West syndrome and children with idiopathic generalized epilepsy, reported complete seizure cessation in 18.6% of partial-onset seizures and in 17.3% of generalized seizures.

Anecdotal case reports described favourable effects of vigabatrin in neonatal seizures due to Ohtahara's syndrome [105] and in Landau–Kleffner syndrome [106]. A number of uncontrolled studies also explored the potential value of vigabatrin in Lennox–Gastaut syndrome, and results have been controversial. The study by Livingston *et al*. [101] cited above included 26 children with Lennox–Gastaut syndrome, and a good seizure response was observed in less than 30% of these cases [101]. Similar findings were reported in Asian children [107]. Only a few children with Lennox–Gastaut syndrome have been included in other studies, and most have not been regarded as treatment successes. In a retrospective assessment of children who had been started on vigabatrin, gabapentin and lamotrigine 10 years earlier, children with myoclonic–astatic epilepsy or Lennox–Gastaut syndrome were found to have done better on lamotrigine than on the other drugs [99]. More favourable results were found in a retrospective 3-year study, reporting a ≥50% reduction in seizure frequency in 40% of patients with Lennox–Gastaut syndrome, although myoclonic seizures worsened in this patient group [108]. A good response in Lennox–Gastaut syndrome was reported in only one open-label study in 20 children, with 85%

of patients showing a ≥50% decrease in all seizure types, except for myoclonic seizures which tended to increase [109]. The precipitation or exacerbation of myoclonic seizures, absence seizures and non-convulsive status epilepticus has also been reported by other authors [110,111].

Overall, available data suggest that vigabatrin may have a limited role as add-on treatment of some generalized epilepsy syndromes, but not in patients with myoclonic seizures as the main seizure type. Vigabatrin also carries some risk of aggravating seizures in patients with generalized epilepsy, particularly in children [102,112]. In a long-term follow-up study of a cohort of 196 children with various refractory epilepsies, non-progressive myoclonic epilepsy and Lennox–Gastaut syndrome showed the highest increase in seizure frequency (38% and 29%, respectively) [102].

As with carbamazepine, use of vigabatrin in patients with idiopathic generalized epilepsies, including childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with grand mal on awakening, may result in increased seizure frequency and even lead to absence status or myoclonic status [113,114]. Precipitation and aggravation of myoclonic seizures, myoclonic–astatic and absence seizures have been described particularly in children with Angelman's syndrome [115].

Adverse effects

General overview of adverse effects

If exception is made for visual field constriction, which is discussed in detail below, adverse effects during vigabatrin treatment are usually mild and the drug is relatively well tolerated, even with high doses. In adults and older children, fatigue, drowsiness, dizziness, nystagmus, agitation, amnesia, abnormal vision, ataxia, weight gain, confusion, depression and diarrhoea have been most often reported [74,116]. In children and infants, the most common adverse effects include sedation, drowsiness, insomnia, hyperactivity, agitation, weight gain and hypertonia or hypotonia [41,43,88,103]. Most of these adverse effects are dose related and reversible when the dose is reduced. Discontinuation of therapy because of these effects is necessary only in rare cases [40]. Single observations have also described the occurrence of vigabatrin-induced encephalopathies with stupor, confusion and EEG slowing, one of the cases being in a patient with Alexander's disease [117–119].

An adverse event possibly related to the GABAergic action is an increased incidence of psychosis, sometimes within the context of forced normalization [120]. A retrospective survey of behaviour disorders in 81 patients described 50 cases meeting the criteria for either psychosis ($n = 28$) or depression ($n = 22$) [121]. A comparison with psychotic events in epilepsy patients never treated with vigabatrin suggested that risk factors for vigabatrin-induced psychosis include a more severe epilepsy, a right-sided EEG focus and suppression of seizures. Depression as a treatment-emergent effect of vigabatrin has been associated with a past history of depressive illness [121]. Formal testing of mood disturbances in 73 adults with refractory epilepsy before and under treatment with vigabatrin revealed that mood problems were the main reason for discontinuation [122]. A review of double-blind, placebo-controlled trials of adjunctive vigabatrin therapy in a total of 717 patients with refractory partial epilepsy confirmed that vigabatrin, when compared with placebo, was associated with a significantly higher incidence of depression (12.1% versus 3.5%, $P < 0.001$) and psychosis (2.5% versus 0.3%, $P < 0.028$) [123]. There were, however, no significant differences between vigabatrin and placebo for aggressive reactions, manic symptoms, agitation, emotional liability, anxiety or suicide attempt [123]. Depression and psychosis were usually observed during the first 3 months. Depression was usually mild, and psychosis was reported to respond to reduction or discontinuation of vigabatrin or to treatment with antipsychotic drugs.

Dodrill *et al*. [124] evaluated the effects of vigabatrin on cognitive function in a double-blind, placebo-controlled, adjunctive-therapy, parallel-group dose–response study (1, 3 and 6 g/day) in patients with difficult-to-control partial-onset seizures. At repeated testing with a series of eight cognitive tests, a dose-dependent decrease in performance was detected in only one test (digit cancellation).

Vigabatrin has been reported to cause a significant increase in α-aminoadipic acid levels in plasma and urine, which may mimic α-aminoadipic aciduria, a rare metabolic disease. Therefore, to avoid diagnostic difficulties, when a genetic metabolic disease is suspected, amino acid chromatography should be performed before initiation of vigabatrin treatment [125]. In addition, vigabatrin can interfere with urinary amino acid analysis due to inhibition of catabolism of β-alanine [126].

Visual field constriction

Severe symptomatic and persistent visual field constriction associated with vigabatrin was reported initially in three patients in 1997 [127]. During the subsequent 2 years, additional similar cases of concentric visual field constriction were described in patients with refractory epilepsy receiving adjunctive therapy with vigabatrin [128,129]. A further study in patients on vigabatrin monotherapy confirmed a causal relationship between vigabatrin and a specific bilateral concentric constriction of the visual field [130]. A survey conducted by the manufacturer and involving 335 vigabatrin recipients aged >14 years indicated that 31% of patients [95% confidence interval (CI) 26–36%] had a visual field constriction attributable to vigabatrin, compared with a 0% incidence of visual field constriction (95% CI 0–3%) in an unexposed control group. Other studies in adults have given similar overall prevalences, with a total of 169 of 528 patients diagnosed with vigabatrin-associated field defects (32%; 95% CI 28–36%). Male gender seems to be associated with an approximately twofold increase in the relative risk of developing visual field constriction. The pattern of defect is typically a bilateral, absolute concentric constriction, the severity of which varies from mild to severe [130]. The cumulative incidence increases rapidly during the first 2 years of treatment and within the first 2 kg of vigabatrin intake, usually stabilizing at 3 years and after a total vigabatrin dose of 3 kg. In adults, regular visual field testing should be performed before the start of treatment and at regular intervals during treatment. Patients with pre-existent visual field defects due to other causes should not be treated with vigabatrin.

The prevalence data for vigabatrin-associated visual field constriction in children are contradictory. Disparities are likely to

arise from many causes, including the diversity of the perimetric techniques, the variable cooperation of patients in complying with the testing procedure, the asymptomatic nature of the defect and the relatively small sample sizes. Several studies using Goldmann perimetry or the Humphrey field analyser in patients aged 5–21 years [131–135] reported a prevalence of visual field constriction between 19% [132] and 71% [134]. The number of patients in these studies ranged from 12 to 67. In a larger study, Vanhatalo *et al*. [53] performed Goldmann perimetry tests in 91 visually asymptomatic Finnish children aged 5.6–17.9 years. Visual field constriction was observed in repeated test sessions in 17 children (18.7%), and a significant inverse correlation was found between the temporal extent of the visual fields and the total vigabatrin dose and duration of vigabatrin treatment. The shortest duration of vigabatrin therapy associated with visual field constriction was 15 months, and the lowest total cumulative dose was 914 g. The latter finding is partly in line with data from a previous paediatric study from Korea (n = 67), in which no cases of visual field constriction were found with treatment durations below 2 years and cumulative doses below 10 g/kg [135].

A more recent study by Wild *et al*. [136] analysed perimetric data of 563 paediatric and adult patients with refractory partial epilepsy, stratified by age (8–12 years; >12 years) and exposure to vigabatrin. Group I comprised 201 subjects (including 49 aged 8–12 years) treated with vigabatrin for >6 months, group II had 220 subjects (including 59 aged 8–12 years) previously treated with vigabatrin for ≥6 months who had discontinued the drug for ≥6 months, and group III had 142 subjects (including 35 aged 8–12 years) never treated with vigabatrin. Perimetric testing was performed every 6 months for up to 36 months. In group I, visual field constriction at the last visit with a conclusive examination was diagnosed in 31.2% of patients aged 8–12 years and 41.6% of patients aged ≥12 years, whereas in group II, corresponding rates were 10.3% and 24%, respectively. No case of visual field constriction was detected in group III. Visual field constriction was significantly associated with duration of vigabatrin therapy [odds ratio (OR) 14.2; 95% CI 5.0–40.5], with the mean vigabatrin dose (OR 8.5; 95% CI 2.2–33.2) and with male gender (OR 2.1; 95% CI 1.2–3.7). Visual field constriction was also detected more often with static than with kinetic perimetry (OR 2.3; 95% CI 1.3–4.2). There was a trend for visual field constriction to be less frequent in the younger age groups, but the statistical power of the comparisons was limited by the small size of the subgroups. In conclusion, approximately one-third of patients aged ≥8 years exposed to vigabatrin exhibited visual field defects which were not encountered in unexposed participants. The study did not include infants with infantile spasms.

Preliminary data of a still ongoing prospective long-term follow-up study comprising infants with infantile spasms seem to demonstrate a lower frequency of visual field constriction in children treated with vigabatrin in early infancy (G. Wohlrab, 2008, unpublished). Sixteen children classified as having cryptogenic or symptomatic West syndrome (tuberous sclerosis complex, focal cortical dysplasia) underwent Goldmann perimetric tests at the age of 7.3–15 years. Visual field constriction was detected in two asymptomatic children, in one case repeatedly, while in another lack of co-operation was assumed and repetition of the examination 1 year later showed normal findings. Based on available data, it remains unclear whether younger age is a protective factor against visual field constriction.

Overall, the mechanisms underlying the retinal toxicity of vigabatrin and the associated risk factors have not yet been fully elucidated. The effect may be idiosyncratic in nature [137,138]. A genetic predisposition has been postulated, but studies conducted to date have failed to identify a genetic marker [139]. Total cumulative dose and duration of treatment have emerged as important risk factors in many studies [53,135,136,140], and in at least one study a correlation also emerged with the maximum daily dose [141].

Vigabatrin-induced visual field constriction is generally considered to be irreversible [130]. Reversibility has been reported in few children and adults, verified by repeated examinations [142,143]. However, test results may be unreliable in some patients because of insufficient cooperation, and an improvement in perimetric findings may be an artefact of a learning process.

From a cognitive age of 9 years on, static perimetry seems to be the most sensitive modality for identifying vigabatrin-induced retinal toxicity [132]. Unfortunately, visual field constriction is not ascertainable in infants, young children and patients with severe mental disability. There are no reliable markers for the early detection of visual field defects. Fundoscopy shows no specific abnormalities until the visual field loss is severe. An 'inverse' optic atrophy has been described as a specific marker of vigabatrin toxicity in children [144]. Electroretinography, multifocal electroretinography [145] and field-specific visual-evoked potentials, as described by Spencer and Harding [146], may be useful in monitoring children with mental disability or too young to cooperate. The most consistent electroretinography changes include increased latency of the electroretinography photopic b-wave, reduced or absent oscillatory potential, and abnormalities of the cone function (30 Hz) response. A marked decrease in electroretinography responses from scotopic threshold response has been suggested as early marker of retinal toxicity [147].

Neuropathological findings

Following the discovery of intramyelinic oedema in animal toxicology studies, many investigations have been carried out to determine whether similar changes could occur in humans. A report in 2008 described six vigabatrin-treated infants with infantile spasms, four of whom were severely hypotonic, in whom MRI with diffusion-weighted imaging showed a transient decrease of diffusion in subcortical structures [148]. These abnormalities were considered to be probably related to the epileptic encephalopathy, although a causative role of vigabatrin could be more likely based on findings from subsequent studies. In particular, a large recent retrospective study evaluated 332 MRI examinations from 205 infants with infantile spasms (aged 2 years or less), 93 of whom had received vigabatrin as initial or subsequent therapy [148]. In this population, the prevalence of prespecified MRI abnormalities (defined as any hyperintensity on T_2-weighted or FLAIR sequences with or without diffusion restriction not readily explained by a radiographically well-characterized pathology) was significantly higher in vigabatrin-treated patients than in vigabatrin-naive patients (22% vs. 4%; $P < 0.001$). The MRI

abnormalities were considered asymptomatic. Of nine vigabatrin-treated subjects with at least one subsequent MRI, resolution of MRI abnormalities occurred in six, four of whom had stopped taking vigabatrin while two were still on the drug. The same study also assessed 2074 MRI images from 668 children (aged 2–16 years) and adults (aged > 16 years) with complex partial seizures and found no significant difference in the incidence or prevalence of prespecified MRI abnormalities between vigabatrin-exposed and vigabatrin-naive subjects [149]. The occurrence of vigabatrin-associated MRI abnomalities in infants is documented by two other recent retrospective reports. Pearl *et al*. [150] found that 8 out 23 subjects treated with vigabatrin had MRI abnormalities characterized by new-onset and reversible T_2-weighted hyperintensities and restricted diffusion in thalami, globus pallidus, dentate nuclei, brainstem or corpus callosum. The abnormalities were reversible after discontinuation of vigabatrin. Affected subjects were younger than those unaffected (median age 11 months vs. 5 years) and received a larger dose of vigabatrin (median 170 mg/kg/day vs. 87 mg/kg/day). Milh *et al*. [151] assessed the frequency of vigabatrin-associated MRI abnormalities in 22 infants who had 34 MRI examinations at different time points. Hyperintensity of basal ganglia and brainstem appeared to be transient and maximal at 3 to 6 months after initiation of vigabatrin. All patients were asymptomatic. Overall, available data suggest indicate that vigabatrin does cause reversible MRI abnormalities in an age- and dosage-related manner, with infants being especially vulnerable. The mechanisms and clinical implications, if any, of these changes are at present unclear.

Neuropathological studies have been carried out on patients who died or had epilepsy surgery during vigabatrin treatment [6,116]. These studies assessed 10 post-mortem and 50 surgical samples, with treatment periods up to 108 months. None of the material examined showed evidence of vacuolation.

One study reported MRI evidence of discrete non-haemorrhagic focal lesions in the splenium of the corpus callosum in six patients with epilepsy who had been treated with either vigabatrin or phenytoin [152]. Although in two of the patients the lesions disappeared at a follow-up MRI after withdrawal of vigabatrin or phenytoin, the role of drug treatment in the pathogenesis of the reported lesions is uncertain.

Teratogenic effects

Animal experiments have shown that vigabatrin has no negative influence on fertility or pup development. No teratogenicity was seen in rats at doses up to 150 mg/kg or in rabbits at doses up to 100 mg/kg. However, in rabbits, a slight increase in the incidence of cleft palate at doses of 150–200 mg/kg was observed. Although there are insufficient clinical data to determine the risks associated with fetal exposure to vigabatrin in humans, the use of vigabatrin is not recommended in women of child-bearing potential [153]. In one report of two children examined at the age of 6.1 and 7.9 years, prenatal exposure to vigabatrin in combination with other AEDs did not appear to have resulted in clear-cut neurological or ophthalmological deficits [154]. One of these children had dysmorphic features. The other had several major and minor congenital malformations, but he had been exposed to vigabatrin only after week 16 of gestation.

Current place in therapy

Because vigabatrin is not approved in the USA, the practice parameters published by the American Academy of Neurology and the American Epilepsy Society [155,156] do not contain any information on vigabatrin. On the other hand, vigabatrin has been used in several other countries, initially mostly for the treatment of drug-refractory partial epilepsies, and more recently mainly for the management of infantile spasms.

Infantile spasms, especially those caused by tuberous sclerosis complex, represent the primary current indication of vigabatrin. In our personal experience, doses between 75 and 150 mg/kg/day can be rapidly effective if the treatment is started early after the onset of spasms.

Visual field constriction seems to occur less frequently in the first 2 years of life, but long-term follow-up data in patients treated in this age group are lacking. The risk of visual impairment in patients with infantile spasms may be reduced by limiting the duration of vigabatrin treatment to 6 months [54].

In children, vigabatrin is also a therapeutic option for the adjunctive treatment of partial-onset seizures, with or without secondary generalization, that failed to respond to other AEDs. Although the incidence of vigabatrin-induced visual field constriction is worrisome, in the context of infantile spasms or other intractable seizures, the potential therapeutic benefits must be weighed against the risks. By taking the risk–benefit balance into account, the guidelines from the UK Paediatric Advisory Group on the use of vigabatrin [157] recommend performing visual field examinations with a Goldmann perimeter or a Humphrey field analyser in patients with a cognitive age >9 years before prescribing the drug, and every 6 months during treatment thereafter.

In adults, vigabatrin should be used as add-on therapy for patients with refractory partial epilepsy only when all other appropriate AEDs given alone or in combination have proved ineffective or have not been tolerated. Adults should also undergo visual field testing before and at regular intervals after starting vigabatrin therapy. In the presence of many alternative AEDs for the treatment of the common epilepsy syndromes, the use of vigabatrin has declined drastically in recent years due to the high risk of retinal toxicity. The recently reported MRI abnormalities in children with infantile spasms raise additional concerns which need further careful investigation in adults as well.

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57 Zonisamide

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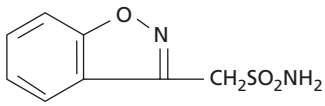

Primary indications	Adjunctive therapy of partial and secondarily generalized seizures. May also be useful as adjunctive therapy in a variety of primary generalized seizure types
Usual preparations	Capsules: 25, 50, 100 mg Tablets: 25, 100 mg Powder (20%)
Usual dosage	Adults: 50 mg/day initially, increased to 100 mg/day after 1 week and 200 mg/day after a further 2 weeks. Further dose increments by 100 mg/day may be indicated at intervals of 1–2 weeks, according to clinical response. Usual maintenance dosages are 200–600 mg/day Children (Japan): 2–4 mg/kg/day, which may be increased gradually every 1–2 weeks to 4–8 mg/kg/day. The maximum daily dose is 12 mg/kg
Dosing frequency	Once or twice daily
Significant drug interactions	Serum zonisamide levels are lowered by carbamazepine, phenytoin and barbiturates
Serum level monitoring	May be useful in selected cases
Reference range	10–40 mg/L
Common/important adverse effects	Somnolence, dizziness, ataxia, headache, attention and concentration difficulties, memory impairment, agitation, irritability, diplopia, confusion, depression, nausea, anorexia, weight loss, nephrolithiasis, hyperthermia, oligohidrosis, skin rashes (including Stevens–Johnson syndrome), blood dyscrasias and other hypersensitivity reactions
Main advantages	Long-term clinical experience (Japan) and suggestive evidence of broad-spectrum efficacy
Main disadvantages	Central nervous system adverse effects, and side-effects from carbonic anhydrase inhibition
Mechanisms of action	Multiple, including blockade of sodium channels, blockade of T-type calcium channels, potentiation of GABAergic transmission, and inhibition of carbonic anhydrase
Oral bioavailability	Almost complete
Time to peak levels	2–6 h
Elimination	Partly by renal excretion, partly by metabolism mediated by CYP3A4, *N*-acetyltransferase and glucuronyl transferases
Volume of distribution	1.1–1.8 L/kg
Elimination half-life	50–70 h (25–40 h in patients co-medicated with enzyme inducers)
Plasma clearance	10–20 mL/h/kg (20–30 mL/h/kg in patients co-medicated with enzyme inducers). Higher clearance values are reported in infants and children
Protein binding	About 50%
Active metabolites	None
Comment	A useful antiepileptic drug with a probable broad spectrum of efficacy

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Introduction

Zonisamide is unusual amongst second-generation antiepileptic drugs (AEDs) in that many patient-years of experience in paediatric and adult populations, in a wide variety of seizure types, had been gained following licensing in Japan (1989) and South Korea (1992) before a series of randomized controlled trials led to regulatory approval as add-on therapy for partial-onset seizures in the USA (2000) and Europe (2005).

Chemistry

Zonisamide (1,2-benzisoxazole-3-methanesulphonamide; molecular formula, $C_8H_8N_2O_3S$) is a white crystalline solid or powder with a molecular weight of 212.2. Zonisamide was discovered through the screening of 3-substituted benzisoxazole derivatives for anticonvulsant activity. With a pK_a of 9.7, the compound is highly soluble in alkaline solutions and is stable in acid, neutral and alkaline solutions [1].

Pharmacology

Activity in animal models and mechanisms of action

Zonisamide is effective in several experimental models of seizures and epilepsy. A mechanism of action similar to that of phenytoin is suggested by activity against maximum electroshock (MES) seizures [1,2] and a reduction of sustained repetitive action potential firing in cultured spinal cord neurones at clinically relevant concentrations [3]. This occurs through blockade of voltage-gated sodium channels and prolonged channel inactivation [4], a mechanism shared with other AEDs including phenytoin, carbamazepine and lamotrigine [5].

In the MES test in rats, rabbits, dogs and monkeys zonisamide shows similar potency to phenobarbital, carbamazepine and phenytoin, with a relatively wide therapeutic window [1,2]. Zonisamide is also similar to these AEDs in preventing the propagation of focal seizure discharges as demonstrated in chemically induced focal cortical seizures in rats [6] and electrically induced focal cortical seizures in cats [7,8].

In other studies, however, zonisamide differed from phenobarbital, carbamazepine and phenytoin in preventing interictal cortical spike discharges in a rat model [9]. Alternative mechanisms of action are also suggested by suppression of cortical spiking similar to that seen with sodium valproate in other animal models [7], and suppression of photosensitive [10] and genetically determined reflex seizures [11]. These additional effects may be mediated in part through inactivation of voltage-gated T-type calcium channels [12], demonstrated at clinically relevant concentrations in cultured rat cortical neurones [13]. Zonisamide also binds to the γ-aminobutyric acid (GABA)–benzodiazepine receptor complex [14], elevates brain levels of the inhibitory neurotransmitter GABA [15], and reduces extracellular release of the excitatory neurotransmitter glutamate [16]. The clinical importance of these effects in mediating zonisamide's antiseizure activity is uncertain, as are dose-dependent effects on dopamine [17] and serotonin [18] turnover demonstrated in rat hippocampi. Zonisamide also has an inhibiting effect on carbonic anhydrase, an action that may contribute not only to the drug's anticonvulsant properties, but also to its adverse effect profile.

Pharmacokinetics

Overview of pharmacokinetic properties

Rapid and almost complete absorption of zonisamide occurs after oral dosing, with time to maximal plasma concentrations (T_{max}) of 2.4–3.6 h and peak plasma concentrations (C_{max}) from 2.3 to 12.5 mg/L in healthy volunteers administered 200, 400 or 800 mg doses [19]. Absorption is delayed in the presence of food (T_{max}, 4–6 h), although the extent of absorption is unaltered [20].

Zonisamide has an apparent volume of distribution (V_d/F) of about 1.1–1.8 L/kg. Binding to plasma proteins is about 50%. Animal studies have shown a wide tissue distribution, with the drug crossing the placenta and accumulating in breast milk at concentrations similar to those in plasma [21]. Zonisamide accumulates in erythrocytes, with a low-affinity binding to cellular proteins in red cells and a saturable high-affinity binding to carbonic anhydrase, a property shared with other sulphonamides [22,23].

Although an approximately linear relationship between serum concentration and dose is reported in some studies, and may be evident within the usual therapeutic dose range, other studies suggested that zonisamide may exhibit non-linear pharmacokinetics, with a greater than proportional increase in serum drug concentration with increasing dose [24,25]. In particular, mean serum concentrations obtained at three doses in a randomized trial were 3.6 mg/L at 100 mg/day, 6.9 mg/L at 200 mg/day and 18.3 mg/L at 400 mg/day [26]. Steady-state serum concentrations are achieved within 15 days, with a modest (about 14%) diurnal fluctuation when the drug is administered on a twice-daily schedule [27]. This is in agreement with an elimination half-life of 50–70 h in the absence of enzyme-inducing co-medication. As discussed below, shorter half-lives (25–40 h) are reported in patients receiving enzyme-inducing AEDs such as carbamazepine, phenytoin and barbiturates. The apparent oral clearance (CL/*F*) of zonisamide is in the order of 10–20 mL/h/kg [25,27,28]. Higher values (20–30 mL/h/kg) are found in patients co-medicated with enzyme inducers.

Zonisamide is extensively metabolized, the predominant pathways being reduction to 2-sulphamoylacetyl-phenol (SMAP) by the cytochrome P450 (CYP) enzyme CYP3A4 [29], acetylation to *N*-acetylzonisamide and, to a lesser extent, direct glucuronidation. These metabolites are devoid of anticonvulsant activity. Urinary recovery is accounted for by unchanged drug (approximately 15–30%), SMAP glucuronide (about 50%), and *N*-acetylzonisamide and zonisamide glucuronide (20%) [21,30,31].

Pharmacokinetics in special groups

Information on the pharmacokinetics of zonisamide in special groups is limited. The half-life of zonisamide in three newborns exposed transplacentally to the drug has been found to be in the range of 60–109 h [28]. In a Japanese study of four infants aged

3 months to 1 year, zonisamide CL/*F* values at steady state were about 50% higher than those reported in 6-year-old children, and at least twofold higher than those reported in 12- to 15-year-old adolescents [28]. In largely uncontrolled paediatric studies, weight-adjusted doses reported to be effective and well tolerated were greater than those described in randomized trials in adults, consistent with zonisamide clearance values being higher in children than in adults [32]. Indeed, available evidence suggests that zonisamide CL/*F* values in children are 20–100% higher than in adults [28].

A study in healthy elderly volunteers suggested that no pharmacokinetic changes requiring dose adjustments occur in this population [30]. However, since no patient in that study was above 71 years of age, these findings may not be applicable to subjects in older age groups.

Detailed studies in patients with hepatic or renal disease are not available, although a single dose study in volunteers showed that clearance is significantly reduced in patients with renal impairment [20,31], with a 35% increase in area under the plasma concentration curve (AUC) at creatinine clearance values <20 mL/min [31].

Drug interactions

Like most other second-generation AEDs, zonisamide has an advantage over older agents in that it does not induce or inhibit the hepatic microsomal enzymes responsible for drug metabolism. In patients on monotherapy, the introduction of zonisamide as add-on treatment at a dose of 400 mg/day did not affect the steady-state serum concentrations of carbamazepine [33], valproic acid [34], phenytoin [35] or lamotrigine [36]. Likewise, zonisamide does not appear to affect, to a major extent, the pharmacokinetics of other medications. In particular, following administration of a combined oral contraceptive, the serum levels of ethinylestradiol and norethisterone have been shown to be unaltered by doses of zonisamide up to 400 mg/day [37]. Since zonisamide is a weak inhibitor of P-glycoprotein (P-gp), however, caution is advised when starting or stopping zonisamide treatment in patients receiving drugs which are P-gp substrates (e.g. digoxin, quinidine), since there is a theoretical possibility that the serum concentrations of the latter may change [31].

Since zonisamide is metabolized by CYP3A4, inducers of this enzyme increase zonisamide clearance. Phenytoin, carbamazepine and phenobarbital shorten the elimination half-life of zonisamide to 25–40 h, so that steady-state serum zonisamide concentrations are achieved within a week in patients co-medicated with enzyme inducers [33,35,38]. No clinically significant effects on zonisamide clearance or half-life were demonstrated with the co-administration of valproic acid or lamotrigine [34,36], or the enzyme inhibitors cimetidine (1200 mg/day) [39] or ketoconazole (400 mg/day) [31].

Since both zonisamide and topiramate exhibit carbonic anhydrase inhibitory activity, the possibility of an adverse interaction between these drugs, particularly an increase in the incidence of renal stones, has been raised. No renal calculi were identified in 59 patients exposed to both zonisamide and topiramate for up to 135 weeks in US and European clinical trials, while one case of nephrolithiasis was reported during postmarketing surveillance in the USA [40].

Serum level monitoring

Although serum zonisamide concentrations can be measured by enzyme-linked immunoassay or high-performance liquid chromatography [41], the relationship between serum concentrations and efficacy is not sufficiently characterized to recommend extensive monitoring in routine clinical practice [42]. In one randomized trial, serum concentrations in patients receiving zonisamide 400 mg/day were in the order of 16.5–21.3 mg/L, although a significant difference in serum concentration was not demonstrated between responders and non-responders, as determined by a 50% reduction in seizure frequency [26]. In two flexible-dose studies, most patients received 400–600 mg/day as a single or twice-daily dose, aiming at achieving steady-state concentrations in the 20–30 mg/L range [43,44]. A recent position paper compiled by a commission of the International League Against Epilepsy [45] proposed for zonisamide a reference range of 10–40 mg/L, based on a review of studies published to date. It was emphasized, however, that there is a wide variability in the concentrations associated with an optimal response, and that concentrations associated with a good response in some patients may be associated with adverse effects in others.

Efficacy

Randomized controlled trials

Published data from randomized double-blind placebo-controlled trials provide evidence of zonisamide's efficacy as add-on therapy in patients with partial and secondarily generalized tonic–clonic seizures. Four multicentre studies, two each in the USA [26,43] and Europe [44,46], included 845 patients with refractory partial-onset seizures (Table 57.1).

Two randomized placebo-controlled trials of similar design included patients aged 17 years or older with four or more partial seizures per month and receiving up to two or three AEDs [43,44,47]. The trials included an 8- to 12-week baseline assessment followed by a 12-week treatment phase during which zonisamide dose was adjusted by an unblinded observer to achieve plasma concentrations in the range of 20–30 mg/L. Median daily doses of 430 mg (as a single daily dose) and 530 mg were achieved [47], and zonisamide produced a significantly greater reduction in median seizure frequency than placebo for complex partial and for all seizure types in both studies.

In another trial conducted with a fixed-dose design in 20 centres in the USA, a significant reduction in median frequency of all seizures (the primary outcome measure) and in responder rate (≥50% reduction in seizure frequency compared with baseline) was reported for zonisamide 400 mg/day during the last 5 weeks of treatment when compared with placebo (seizure reduction 40.5% versus 9%, $P < 0.001$; responder rate 42% versus 22%, $P < 0.05$) [26]. A modified intention-to-treat (ITT) analysis included 170 of 203 randomized subjects, and a secondary endpoint analysis allowed comparison during the titration phase

between parallel groups treated with zonisamide 100 mg/day or 200 mg/day, or placebo. Within the limitations of this analysis, significant reductions in median seizure frequency at the lower doses were seen compared with placebo treatment (zonisamide 200 mg/day, 20.4% versus 4.0%, $P < 0.01$; zonisamide 100 mg/day, 24.7% versus 8.3%, $P < 0.05$).

A multicentre trial carried out in 18 European countries and in South Africa investigated zonisamide as adjunctive treatment in 351 patients aged 12 years or older with refractory partial-onset seizures [46]. To assess the dose–response relationship, patients were randomized to placebo or zonisamide 100 mg/day, 300 mg/day or 500 mg/day in the ratio 2:1:1:2, with a 6-week dose titration and an 18-week fixed-dose assessment phase. The primary outcome measures were median percentage changes in seizure frequency from baseline and responder rates (≥50% reduction in seizure frequency compared with baseline) for complex partial seizures. Compared with placebo, zonisamide 500 mg/day was associated with a significant reduction in median complex partial seizure frequency (51.2% versus 16.3%, $P < 0.001$) and a higher responder rate (52.3% versus 21.3%, $P < 0.001$). Significant benefits were also seen for all partial and all seizure types at this dose. Zonisamide 300 mg/day significantly reduced the frequency of all seizures, but not the frequency of complex partial seizures, although this dose group had a low baseline seizure rate and relatively few patients following randomization [46]. A significant association between zonisamide dose and responder rate was demonstrated, and an odds ratio of 4 (for a ≥50% reduction in seizure frequency) was calculated for zonisamide 500 mg/day against placebo [47].

Uncontrolled studies

Uncontrolled observations including small case series and retrospective reports are available in patients with a variety of less common epilepsy syndromes or primary generalized seizures who received treatment with zonisamide.

In two retrospective series, 22 patients with refractory or newly diagnosed juvenile myoclonic epilepsy were treated with zonisamide (13 as monotherapy), and the majority achieved >50% seizure reduction, including two patients who became seizure free on combination therapy. Complete control of generalized tonic–clonic, myoclonic and absence seizures was reported for nine, eight and five patients respectively treated with zonisamide monotherapy [48,49]. In another patient with juvenile myoclonic epilepsy described in a separate case report, seizure control was accompanied by abolition of spike–wave discharges in the EEG [50].

Ten of 30 patients with progressive myoclonic epilepsy who received zonisamide as adjunctive therapy for up to 16 weeks in an open-label study were reported to have achieved a ≥50% reduction in myoclonic seizure frequency [51]. The majority of seven further patients with Unverricht–Lundborg or Lafora body disease were reported to have obtained sustained clinical benefit with follow-up periods of 2 or more years [52].

Extensive clinical experience has been reported from Japan, where zonisamide is licensed for a broad range of seizure types in both adults and children, and as monotherapy [25]. Pooled data from pre-registration studies and postmarketing surveillance include controlled, open-label and unpublished trials in patients with partial seizures, primary generalized tonic–clonic seizures, tonic, atonic and absence seizures and other seizure types [25,53,54]. High responder rates (≥50% reduction in baseline seizure frequency), in some cases exceeding 80%, are reported in the majority of these studies for partial and some generalized seizure types, and for over 400 patients receiving zonisamide monotherapy. This pooled dataset includes over 200 children with Lennox–Gastaut syndrome (up to 35% responders) and 122 cases of West syndrome (29% responders) [53,55]. These observations point to the need for randomized controlled trials of zonisamide against placebo and standard therapy in these treatment-resistant forms of severe childhood epilepsy.

Adverse effects

Common adverse effects

Treatment-related adverse events were reported in 61% of 498 zonisamide-treated patients and in 49% of 350 placebo-treated patients in a pooled analysis of patients enrolled in randomized placebo-controlled trials (Table 57.1) [47]. Central nervous system (CNS)-related side-effects were the most frequently recorded adverse events in these studies. Somnolence or dizziness in up to 18% of patients occurred significantly more frequently than in placebo-treated control subjects, with headache, nausea or anorexia, abnormal thinking (a code term used to indicate attention or concentration difficulties) or confusion, agitation or irritability, depression, memory impairment, diplopia and ataxia also reported in 10% or more of zonisamide-treated subjects in individual trials [26,43–46]. Adverse events were most often reported at zonisamide doses above 400 mg/day and with rapid dose titration. Open-label extension studies including patients from short-duration randomized or uncontrolled trials with up to 9 years' follow-up demonstrated a similar pattern of CNS adverse effects (Table 57.2) [56,57]. Weight loss has also been reported in some patients.

Dizziness or incoordination, impaired concentration and anorexia or nausea most often led to zonisamide withdrawal, with treatment retention rates at 1, 2 and 3 years of 65%, 45% and 29% respectively [57].

Other adverse effects

Although zonisamide differs structurally from arylamine sulphonamide antibacterials, zonisamide treatment is contraindicated in patients with a known hypersensitivity to sulphonamide compounds. Reports of skin rash are uncommon, although 49 cases of Stevens–Johnson syndrome or toxic epidermal necrolysis identified through postmarketing surveillance in Japan gives an estimated risk of 4.6 cases per 100 000 patient-years exposure [20]. Very rare cases of aplastic anaemia, agranulocytosis, other blood dyscrasias and other hypersensitivity reactions have also been reported [31].

Symptomatic renal calculi were identified in 9 of 626 (1.4%) patients taking part in randomized controlled trials or open-label extension studies and in 15 of 1296 (1.2%) patients taking zonisamide for up to 8.7 years in the USA and Europe [40]. Although an overall low incidence of renal stones, similar to the

Table 57.1 Zonisamide: summary of efficacy and adverse events in randomized placebo-controlled double-blind adjunctive therapy trials in patients with refractory partial-onset seizures.

	Schmidt *et al*. [44]		Sackellares *et al*. [43]		Faught *et al*. [26]				Brodie *et al*. [46]			
Number of subjects	139		152		203				351			
Blinded treatment period evaluated [weeks]	12 weeks		12 weeks		5 weeks				18 weeks			
	Placebo	*Zonisamide*	*Placebo*	*Zonisamide*	*Placebo*	*Zonisamide*			*Placebo*	*Zonisamide*		
Zonisamide daily dose		Median 430 mg		Median 530 mg		100 mg	200 mg	400 mg		100 mg	300 mg	500 mg
All seizures												
Number of evaluable patients	64	67	74	78	72	56	55	98	112	54	45	101
Median baseline seizure frequency per 28 days	NA	NA	10.6	9.1	13.0	11.2	13.0	12.1	5.7	6.3	5.9	6.2
Median change in seizure frequency from baseline	3%	–22.5%*	6.60%	–25.5%***	–9%	–24.7%*	–20.4%**	–40.5%***	–18.10%	–19.20%	–41.8%***	–51.3%***
Responder rate (patients with at least 50% seizure reduction)	9.40%	29.9%*	16.20%	28.20%	22%	25%*	25%*	42%**	17.90%	29.60%	42.20%	52.5%***
Seizure free	1	4 (6.0%)	NA	NA	2 (2.8%)	NA	NA	6 (6.1%)	2 (2%)	NA	NA	6 (5%)
Complex partial seizures												
Number of evaluable patients	63	66	72	78	72	56	55	98	89	40	25	86
Median baseline seizure frequency per 28 days	8.8	12	7.8	8	7.0	6.2	8.0	7.1	5.7	6.3	2.9	6.2
Median change in seizure frequency from baseline	3.9%	–27.7%*	–0.50%	–27.4%***	NA	–33.3% vs. –8.6%(placebo)**	–17.2% vs. –9.8%(placebo)	NA	–16.30%	–9.90%	–40.10%	–51.2%***
Responder rate (patients with at least 50% seizure reduction)	12.7%	30.3%*	13.90%	30.8%*	NA	NA	NA	NA	21.30%	22.50%	36.00%	52.3%***
Percentage of patients with adverse events	28%	59%	50%	60%*	NA	NA	NA	NA	68.30%	67.90%	70.90%	81.40%
Number of discontinuations due to adverse events	0	2 (3.0%)	1 (1%)	12 (15%)	8.20%	NA	NA	10%	12 (10%)	1 (1.8%)	10 (18.2%)	32 (27.1%)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 57.2 Summary of adverse events occurring in 10% or more of patients included in long-term studies with zonisamide.

Adverse effect	Percentage of patients affected	
	Leppik *et al.* [56] (*n* = 1207)	Wroe *et al.* [57] (*n* = 318)
Somnolence	22	15
Dizziness	21	17
Anorexia	17	–
Tiredness/fatigue	15	12
Nausea	13	11
Headache	12	23
Confusion	12	–
Mental slowing	11	–
Agitation/irritability	11	–
Diplopia	11	–
Memory problems	10	–
Nasopharyngitis	–	16
Weight loss	–	14
Diarrhoea	–	10

background population risk, is reported through postmarketing surveillance in the USA and Japan, an analysis of individual case reports identifies either a personal or family history of renal stones, or pre-existing renal or urinary tract abnormalities, as possible predisposing risk factors for stone formation. Such potentially at-risk individuals should be advised to maintain an adequate fluid intake if treated with zonisamide [40].

Hyperthermia and oligohidrosis have been reported as rare but potentially serious adverse events, with an estimated risk of 20 cases per 100 000 patient-years exposure in the USA. Children are usually affected, and hot weather or dehydration are potential risk factors [20,58,59].

Teratogenicity

Information published in the Japanese literature and available in the manufacturer's database demonstrates teratogenicity in several animal species. Cardiovascular defects in particular, but also skeletal and other abnormalities, and fetal death are described at serum concentrations comparable to those seen after therapeutic dosing in humans [60,61, cited in 20].

Data from the manufacturer on 26 births or pregnancies in which zonisamide was taken have been reported, and include the earliest experience in Japanese patients [53]. A ventricular septal defect was recorded in one of seven births following fetal exposure to zonisamide monotherapy. Malformations occurred in 2 of 19 cases exposed to polypharmacy during pregnancy, including an atrial septal defect after phenytoin, carbamazepine and zonisamide exposure, and a malformation of the brain and skull after phenytoin and zonisamide exposure. The latter may have been the same case described as an encephaly in an earlier report [62].

Given the experimental evidence of teratogenicity, and since information regarding the safety of zonisamide in pregnancy is extremely limited, zonisamide should preferably be avoided in women of child-bearing potential or used only in the presence of effective contraception.

Place in current therapy

Place in therapy

Since current AED treatment fails to provide complete seizure control without unacceptable adverse effects in up to 35% of patients with epilepsy [63], there is a place for new pharmacological treatments with novel mechanisms of action and improved tolerability. Zonisamide exhibits seizure-suppressing activity similar to that of phenytoin or carbamazepine in animal models, although experimental data and some clinical observations suggest the potential for a broader spectrum of efficacy.

Short-term placebo-controlled trials have established zonisamide as an effective adjunctive therapy in patients with refractory partial-onset seizures. Since the drug is reasonably well tolerated, has few interactions with other medications and the potential for once- or twice-daily administration, it offers a useful additional therapeutic option in this patient population. Extensive clinical experience and open-label observational studies provide evidence for sustained efficacy and suggest that serious adverse effects are uncommon. Further studies directly comparing zonisamide with other established and new AEDs, particularly as monotherapy, are required to fully determine the drug's place in clinical practice.

Uncontrolled observational studies and retrospective case series have suggested that zonisamide may be of benefit in some severe paediatric epilepsy syndromes, or rare seizure disorders for which current therapies are largely ineffective. These observations should be tested in well-designed clinical trials.

Dose, titration rate and laboratory monitoring

Zonisamide has demonstrated efficacy in adults, most clearly at doses above 200 mg/day. Effective doses in routine clinical practice are commonly in the range of 200–600 mg/day. Serum drug levels are not indicated routinely. Common CNS side-effects, particularly drowsiness, dizziness and nausea, are much more likely with rapid dose titration, and it is therefore recommended that zonisamide be started at a dosage of 50 mg/day (preferably in two divided doses), to be increased to 100 mg/day after 1 week [31]. Thereafter, the total daily dose may be increased by no more than 100 mg every 2 weeks.

In Japan, approved dose regimens for children are 2–4 mg/kg/day initially, to be increased gradually every 1–2 weeks to 4–8 mg/kg/day. The maximum daily dose is 12 mg/kg.

Although serious adverse effects are rare and routine laboratory monitoring is not required, treating clinicians should be alert to the development of unexplained skin rashes or haematological abnormalities. Patients with known risk factors for renal calculi should be advised to maintain an adequate fluid intake, and parents of children treated with zonisamide should be made aware of the need to avoid dehydration and overheating.

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58 Other Drugs Rarely Used

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Introduction

This chapter focuses on a number of medications that are not frequently used in the treatment of epilepsy. However, there is no doubt that some of these drugs may be useful in special clinical situations. A number of the compounds discussed have been used primarily as antiepileptic drugs (AEDs) for many decades, while others include some agents licensed mostly for other indications. The most important features of each drug are briefly discussed, with special emphasis on their potential clinical use.

Allopurinol

Developing AEDs that are specifically tailored to a patient's individual biochemistry has long been a goal of neurology. Allopurinol was introduced initially by Coleman *et al.* [1] for the treatment of epilepsy in patients who also had hyperuricaemia. Subsequently, DeMarco and Zagnoni [2] reported that the drug was also effective in patients with epilepsy without hyperuricaemia.

Chemistry

Allopurinol (4-hydroxypyrazolo-3,4-D-dipyramidine) is a structural analogue of hypoxanthine and has a molecular weight of 136.1.

Mechanisms of action and activity in experimental models of seizures and epilepsy

Allopurinol inhibits the enzyme xanthine oxidase with subsequent reduction of uric acid in the blood, but the mechanism of its antiepileptic action is unclear. It is also unknown if the antiepileptic effect is based on allopurinol only, or on oxypurinol, the main and active metabolite, or on both.

Experimental studies have shown that allopurinol suppresses epileptiform activity induced by penicillin in the rat hippocampus [3]. Hoppe *et al.* [4], on the other hand, did not find anticonvulsant effects in a model of oxygen-induced seizures in mice. The effect of allopurinol on seizures kindled in the feline hippocampus has been investigated by Wada *et al.* [5], employing two different doses (5 and 50 mg/kg). It was found that the high dose had a significant effect on behavioural seizures, but the duration of afterdischarges was not affected by either dose. Thus, allopurinol is an effective anticonvulsant in some models. The underlying mechanisms of action may be due to an effect on excitotoxicity. Allopurinol inhibits tryptophan-2,3-dioxygenase, which causes a reduction in quinolinic acid, an endogenous glutamate analogue with proconvulsant action. It has been postulated that this is the underlying mechanism of at least part of its antiepileptic effect [6]. In addition, allopurinol appears to suppress free radical generation [7] and to act as an adenosine agonist [8].

Pharmacokinetics

Allopurinol is quickly absorbed from the gastrointestinal tract and its bioavailability is about 80%. After oral intake, peak serum drug levels are reached within 30–120 min. The peak levels of oxypurinol, the active metabolite of allopurinol, are found 2–5 h after both oral and intravenous administration [9].

Allopurinol has an elimination half-life of about 1.2 h. The half-life of the active metabolite oxypurinol is in the order of 17–30 h [10]. About 20% of an allopurinol dose is excreted in faeces within 48–72 h after oral intake. The main active metabolite oxypurinol is completely excreted in urine without further metabolism [11].

Drug interactions

Various reports [2,12,13] suggest that plasma concentrations of most AEDs are not affected by the additional administration of allopurinol. There is, however, one report of allopurinol-induced elevation of carbamazepine levels [14].

Allopurinol shows a number of important interactions with drugs used for conditions other than epilepsy. In particular, potentially fatal interactions may occur when allopurinol is coprescribed with azathioprine or 6-mercaptopurine. The metabolism of azathioprine is inhibited by allopurinol, and this combination requires a reduced dosage of azathioprine. A similar interaction occurs with mercaptopurine, which is used in the treatment of leukaemia and is also a metabolite of azathioprine.

Clinical efficacy

The efficacy of allopurinol in epilepsy is controversial. Sander and Patsalos [15] did not find the drug effective in intractable epilepsy, nor did So and Ptacek [16]. Other clinical trials suggest that allopurinol is most effective in patients with focal epilepsy and secondarily generalized seizures. DeMarco and Zagnoni [2,12] found it effective in generalized tonic–clonic seizures. Tada *et al.* [13] reported the antiepileptic efficacy of allopurinol in generalized tonic–clonic seizures and focal epilepsy, but found it ineffective in Lennox–Gastaut syndrome. Conversely, Marrosu *et al.* [17] found it particularly effective in Lennox–Gastaut syndrome, but not in other forms of epilepsy.

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Zagnoni *et al.* [18] assessed allopurinol (150 mg/day for children weighing <20 kg and 300 mg/day for other patients) in a double-blind, randomized, placebo-controlled, cross-over trial in 84 patients with seizures refractory to standard AEDs. Allopurinol significantly reduced the number of total seizures ($P < 0.005$) and of secondarily generalized seizures ($P < 0.0015$). Median frequency reduction for total seizures was 10.5% and 27.9% for secondarily generalized seizures. Togha *et al.* [8], in a more recent double-blind randomized adjunctive therapy trial, compared allopurinol (titrated up to 100 mg three times a day) with placebo, each in addition to pre-existing AEDs, in 32 patients with refractory epilepsies. Various seizure types were included: complex partial, tonic–clonic and generalized 'atonic' seizures. A significant reduction in seizure frequency in the allopurinol group compared with controls was reported. Two months after initiation of the study, a reduction in seizure frequency of more than 50% in half of the patients in the allopurinol group was seen. However, this trial was very small and results might have been influenced by selection bias. Another double-blind, placebo-controlled cross-over trial with allopurinol as add-on therapy in childhood refractory epilepsy had less favourable results [19]. Seventeen patients received allopurinol and matched placebo for 12 weeks (10 mg/kg/day during the first week and 15 mg/kg/day thereafter, with a washout period of 2 weeks between treatment phases). The total number of seizures was reduced by 50–98% in four patients (23.5%) and by 25–49% in another four (23.5%). However, the number of seizures remained unchanged in five patients (29.4%) and worsened in four (23.5%). A mean follow-up of 10 months in responders did not show any relevant efficacy of allopurinol as an adjuvant therapy for refractory epilepsy, even at high doses. Thus, further studies are needed to determine the value of allopurinol as an AED.

Allopurinol is used as an add-on therapy with dosages of up to 300 mg/day, given in two or three divided doses.

Adverse effects

Adverse effects, in general, are mild and may occur in up to 25% of patients. Those most common include headache, diarrhoea and malaise [15], decreased appetite, drowsiness and abdominal pain [13]. It is unclear whether adverse effects are dose dependent.

Place in current therapy

Allopurinol may play a minor role as an adjunctive therapy for refractory epilepsy.

Bromide

Bromides were the first effective AEDs [20] but their use in the treatment of epilepsy dropped dramatically after the introduction of phenobarbital and phenytoin [21]. Since then, bromides have gained a reputation of having a very narrow target range and being less effective than other AEDs [22]. However, there are also studies which have shown that bromides are more effective than other drugs in the treatment of special syndromes such as refractory tonic–clonic seizures of childhood [23–25], severe myoclonic epilepsy in infants [26] and malignant migrating partial seizures in infancy [27].

Chemistry

Bromide is formulated in various salts. In clinical practice the salts most commonly used are sodium bromide, calcium bromide and ammonium bromide. Bromine itself is a non-metallic element which does not occur in pure form in nature because of its high reactivity.

Mechanisms of action and activity in experimental models of seizures and epilepsy

The mechanisms by which bromides produce antiepileptic effects are still not entirely clear. According to Balcar *et al.* [28], bromide does not affect the γ-aminobutyric acid (GABA)ergic inhibitory system. This was indicated by a lack of changes in the metabolism or transport of GABA and also by unchanged characteristics of the receptor-associated GABA binding sites under acute or chronic bromide exposure. In contrast, Suzuki *et al.* [29] have shown that bromide potentiates GABA-activated currents in cultured cerebral neurones. To clarify such contradictory results, the effect of the bromide on GABAergic inhibition was tested in a paired-pulse protocol and on inhibitory postsynaptic currents [30]. A significant increase in paired-pulse inhibition was seen in a paired-pulse stimulation protocol used to monitor the efficacy of GABAergic inhibition at concentrations of 5 mmol sodium bromide. This finding was confirmed in whole-cell patch clamp recordings from cultured hippocampal neurones showing an increase in inhibitory postsynaptic current amplitude.

It has also been suggested that bromide may interact with the enzyme carbonic anhydrase, resulting in extracellular acidosis and consequent inhibition of epileptiform activity [31]. This prompted a study to compare the effect of both the carbonic anhydrase inhibitor acetazolamide and sodium bromide on extracellular pH changes at rest and following electrical stimulation [30]. Using pH-sensitive microelectrodes, different effects of sodium bromide as compared with those of acetazolamide on extracellular pH under control conditions and after stimulation were seen. Acetazolamide at 1 mmol caused a reversible acidification of ΔpH (0.2 ± 0.14 at rest), whereas no change on extracellular pH was seen with 5 mmol sodium bromide. Acetazolamide increased the transient alkalosis induced by repetitive stimulation of the stratum radiatum in area CA1 and reduced the subsequent acidosis. Sodium bromide also increased the alkalosis but had no effect on the subsequent acidosis. The results indicate that the antiepileptic properties of bromide are unlikely to be caused by its effect on extracellular pH.

In preclinical studies, Grewal *et al.* [32] demonstrated the anticonvulsant potency of sodium bromide using six different procedures – four electrical and two chemical. The electrical procedures included the maximal electroshock seizure pattern test, the minimal electroshock seizure pattern test, the minimal electroshock seizure pattern in hyponatraemic (low threshold) mice test and a test in which unidirectional currents of four times threshold intensity are delivered. The chemical procedures were based on pentylenetetrazole injections. It could be demonstrated that sodium bromide is effective in all tests employed and modifies seizure pattern as well as elevates seizure threshold.

Using combined rat hippocampus–entorhinal cortex slices, Meierkord *et al.* [30] analysed the effects of sodium bromide on

four types of epileptiform discharges in two different models of epilepsy, the low-Ca^{2+} and the low-Mg^{2+} model. Sodium bromide concentration-dependently reduced the frequency and finally blocked the low-Ca^{2+}-induced discharges. Low-Mg^{2+}-induced short recurrent discharges were also reduced in a concentration-dependent manner. In the entorhinal cortex the frequency of seizure-like events was reduced by 3 and 5 mmol and the discharges were blocked by 7 mmol sodium bromide. Also, the late recurrent discharges in the entorhinal cortex which do not respond to most clinically employed AEDs were reduced by concentrations of 10 and 15 mmol and were completely blocked by 30 mmol sodium bromide (Fig. 58.1).

Clinical pharmacokinetics

Bromide is completely absorbed from the gastrointestinal tract and distributed throughout the body in an almost identical fashion to chloride [33]. It replaces chloride in extracellular fluids and the equivalent amount of chloride is excreted. Intracellularly, bromide is found largely in red blood cells. The rate of distribution to the cerebrospinal fluid, gastrointestinal tract and muscle is slower. The ion easily crosses the placenta. Via breast milk, it can cause hypotonia and irritability in infants when used during nursing [34,35].

Bromide is excreted unchanged by the kidneys. In the distal tubule there is a competitive reabsorption of chloride and bromide, a fact that can be exploited in cases of bromide intoxication as administration of chloride will speed up bromide excretion. The elimination half-life ranges between 10.5 and 14 days [34], so the steady-state concentration is reached 40–50 days after treatment initiation [36].

Drug interactions

Bromide does not bind to plasma proteins and there is no evidence that it induces or inhibits the enzymes responsible for the metabolism of other AEDs. For these reasons, no metabolic drug interactions are expected. However, bromide may enhance the central nervous system (CNS)-depressant effects of other AEDs.

There is a drug–food interaction with the chloride ion. When sodium chloride is ingested in the form of table salt, the chloride ion in sodium chloride displaces the bromide ion so that the bromide does not accumulate as expected. Therefore, it is recommended that the ingestion of sodium chloride is held fairly constant during administration of bromides.

Clinical efficacy

There are no randomized, placebo-controlled trials on the efficacy of bromides in epilepsy. Much of the available literature is in the form of single case reports and anecdotal information. Most therapeutic efforts and recent reports focus on the treatment of infants, children and adolescents.

In 1953, Livingston and Pearson [37] reported on the effects of triple bromide elixir (ammonium bromide, potassium bromide and sodium bromide) in 196 children with epilepsy. Sixty-one patients had complete seizure control, 39 were markedly improved (75% reduction in number of seizures), 15 had less than a 50% improvement and 81 did not improve. Of the various seizure types, bromides appeared to be most effective against generalized tonic–clonic, partial, myoclonic and akinetic seizures. There was no beneficial effect on absence seizures. Dreifuss and Bertram [36] reported six patients treated with bromides. Two patients with complex partial seizures and two patients with generalized tonic–

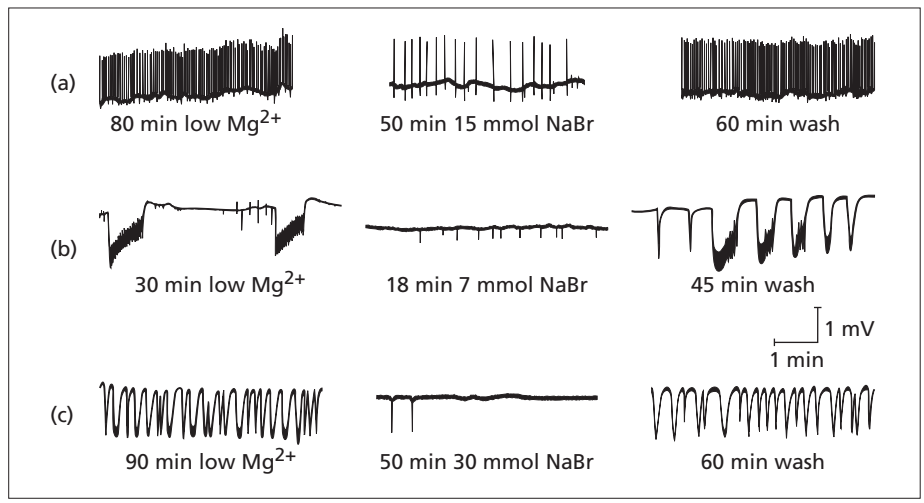

Fig. 58.1 Effects of sodium bromide (NaBr) on different types of spontaneous epileptiform activities. (a) Effects on low-Mg^{2+}-induced short recurrent discharges (SRDs). Low-Mg^{2+}-induced activity in hippocampal area CA1 is characterized by SRDs associated with positive field potentials superimposed by repetitively bursting spikes. Such activity appears following 80 min of Mg^{2+} washout. SRDs in hippocampal region CA1 under 15 mmol sodium bromide are reduced in frequency but not in amplitude, while under 20 mmol SRDs were completely blocked (not shown). The effects on these discharges are reversible. (b) Low-Mg^{2+}-induced seizure-like events. Seizure-like events characterized by tonic- and clonic-like electrographic activity superimposed on slow negative field potentials appear in the entorhinal cortex but not in the hippocampus proper after 30 min of washout of Mg^{2+}. Sodium bromide at concentrations of 7 mmol blocks these discharges reversibly. (c) Effects on low-Mg^{2+}-induced late recurrent discharges. Following prolonged washout of Mg^{2+} (90 min), the seizure-like events in the entorhinal cortex change to late recurrent discharges. Sodium bromide at concentrations of 30 mmol blocks such activity reversibly.

clonic seizures became seizure free. Two patients with absence seizures did not show an improvement. Boenigk *et al.* [23] reported the effects in 68 children and adults. Thirty-three per cent of patients with tonic–clonic seizures of early childhood became seizure free. No improvement in patients with Lennox–Gastaut syndrome was seen.

Woody *et al.* [34] carried out a study in children with different types of epilepsy including photosensitive epilepsy, acquired epileptic aphasia, Lennox–Gastaut syndrome and focal seizures. Six of 11 patients had at least a 75% improvement in seizure control. Three patients had transient improvement, and two had no reduction in seizure frequency. Steinhoff and Kruse [25] reported the results of bromide in 60 patients with generalized tonic–clonic seizures resistant to treatment with standard medication. There was a 50% reduction in seizure frequency in 58% of patients.

Oguni *et al.* [26], in a study on 22 infants with severe epilepsy and various seizure types, saw potassium bromide reduce the frequency of tonic–clonic seizures in 17 of 22 patients. In addition, partial seizures were reduced in all seven patients and myoclonic or absence seizures were also reduced in four patients.

Okuda *et al.* [27] reported complete seizure control in one and 95% reduction in seizure frequency in another infant with malignant migrating partial seizures in infancy. Korinthenberg *et al.* [38] studied potassium bromide in 113 patients (aged 1–20 years) with severe epilepsy manifesting with generalized tonic–clonic seizures. The number of patients who had suffered generalized tonic–clonic seizures during the previous month dropped from 82 to 41, and the median seizure frequency dropped from 4.5 to 0 per month. Of the patients with generalized tonic–clonic seizures during baseline, 49% had none in the last 4 weeks of the study, and another 31% had a reduction by more than 50%.

The usual dosage of sodium bromide in children under 6 years of age ranges from 300 mg twice a day to 600 mg three times a day; over 6 years of age, a dose of 300 mg to 1 g is given three times a day. The therapeutic blood bromide concentration has been reported to range between 10 and 20 mmol/L [34,36].

Adverse effects

Apart from bromide exanthema, adverse effects are generally dose dependent and may be divided into those affecting the gastrointestinal tract, the skin and the nervous system.

Effects on the gastrointestinal tract include anorexia, constipation and weight loss [31]. Pancreatitis as a side-effect of potassium bromide therapy has also been described [39]. In cases of bromism, the tongue may feel coated and sore. When large quantities of bromide salts are ingested, nausea and vomiting may occur [40].

The three main dermatological manifestations are bromide exanthema, acneiform eruptions and bromoderma tuberosum [41]. Acneiform rashes usually occur on the face but may also spread over the neck, chest and arms [36]. If a rash develops, the medication should be discontinued. Bromoderma tuberosum is, in most cases, fully reversible after cessation of the medication. The mechanisms by which the lesions and the associated intraepidermal abscesses are formed are unknown.

Neuropsychiatric adverse effects (bromism) include sedation, action myoclonus, cerebellar signs such as ataxia and dysarthria, decreased libido, dysphagia, decreased tendon jerks, somnolence, tremor and hallucinations [31]. Severe bromism is associated with bromide concentrations above 200 mg/100 mL and manifests as restlessness, headache, delirium and dementia. Other features consist of diminished deep tendon reflexes, loss of pupil reflexes, papilloedema, increased cerebrospinal fluid pressure, slowing on EEG and loss of gag reflex [42].

Place in current therapy

Bromides are no longer a mainstay in the treatment for epilepsy. However, given the fact that bromides are cheap and widely available AEDs with powerful antiepileptic properties, they should have a place as a medication of tertiary choice in severe forms of childhood epilepsy.

Ethotoin

Ethotoin is a phenyl derivative with a structure and mechanism of action similar to phenytoin. Today, it is very rarely used in clinical practice.

Ethotoin has a lower antiepileptic potency than phenytoin and has hypnotic properties; both factors limit its clinical use. It is attractive, on the other hand, because it lacks the adverse effects of gingival hyperplasia and hirsutism. Ethotoin is mostly used as an adjunct in patients with generalized tonic–clonic seizures. Carter *et al.* [43] found it useful in reducing seizure frequency in children with intractable epilepsy. Ethotoin is given in divided doses of 20–40 mg/kg/day.

Adverse effects include ataxia, visual disturbances, rash and gastrointestinal disturbances [44]. Malformations such as cleft lip and cleft palate have been reported in infants born to mothers taking ethotoin [45].

Furosemide

The loop diuretic furosemide has been shown to effectively suppress epileptic activity in experimental studies. Some evidence exists that the drug may also be clinically effective in suppressing epileptic discharges and reducing the frequency of epileptic seizures.

Chemistry

Furosemide is a sulphamoylbenzene derivative of anthranilic acid. Its most important structural characteristic is a carboxide group, while the sulphonamide structure seems to be without pharmacological relevance. The substance appears as a white-yellowish powder and has a molecular weight of 330.74. Furosemide is poorly soluble in water.

Mechanisms of action and activity in experimental models of seizures and epilepsy

In vivo animal data have demonstrated that furosemide terminates self-sustaining status epilepticus induced by chemoconvulsants or electrical stimulation with a delay of 30–90 min [46,47] (Fig 58.2). Such potent anticonvulsant properties are probably based on a number of mechanisms. *In vitro* data suggest that neuronal synchronization is reduced via its inhibitory effect on the $Na^+/K^+/2Cl^-$ co-transport system, resulting in partial preven-

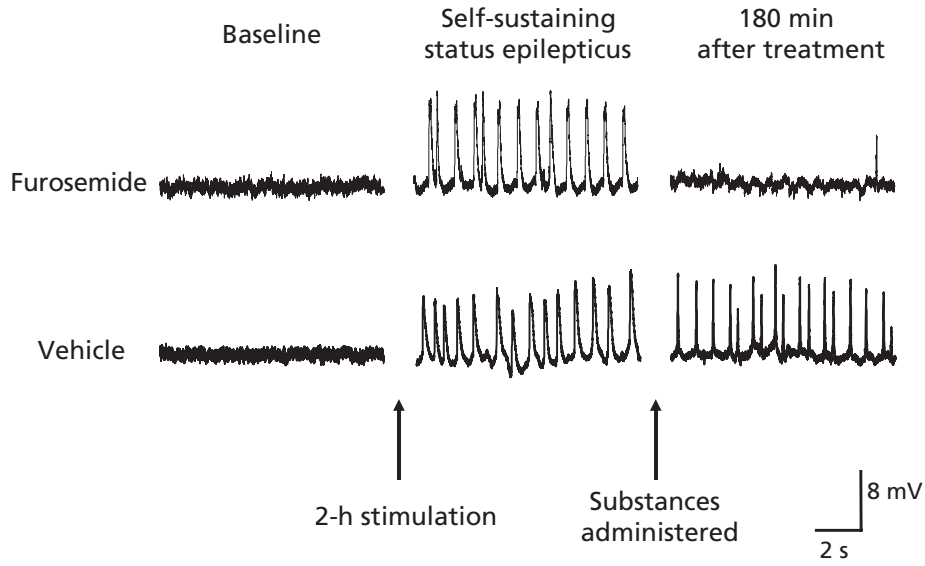

Fig. 58.2 Electrographic recordings from the dentate gyrus *in vivo*. Each trace shows 10 s of the electroencephalogram (EEG) recorded at different points in time. Animals were given furosemide (10 mg/mL) 100 mg/kg intraperitoneally (i.p.) or saline 10 mL/kg i.p. The EEG displays unchanged status epilepticus activity in animals given the vehicle. In contrast, in animals treated with furosemide the ongoing epileptic activity was terminated, apart from occasional spikes. This effect did not occur immediately but in a delayed fashion.

tion of activity-induced extracellular space shrinkage [48]. In addition, reduced neuronal excitability seems to contribute to its anticonvulsant properties [48].

Clinical pharmacokinetics

The oral bioavailability of furosemide is about 50–60%. Peak plasma concentrations are seen about 1 h after oral administration. Furosemide binding to plasma proteins is >95% and the elimination half-life is about 2 h. Furosemide is predominantly excreted unchanged in urine. The only significant metabolite is a glucuronide conjugate.

Drug interactions

Furosemide may cause a modest increase in serum phenobarbital levels [49]. Phenytoin, methotrexate and probenecid may reduce the efficacy of furosemide. If furosemide is co-administered with drugs that prolong the QT interval of the ECG, such as some antiarrhythmics, the risk for ventricular fibrillation is increased. Furosemide may potentiate the antihypertensive effects of many antihypertensive agents and the ototoxicity of aminoglycosides and ethacrynic acid.

Clinical efficacy

In a double-blind placebo-controlled trial, a single intravenous dose of furosemide (40 mg) was found to be as effective as lorazepam (2 mg), clonazepam (0.5 mg) and diazepam (5 and 10 mg) in suppressing interictal spike discharges in the EEG of patients with epilepsy [50]. Interestingly, a subsequent study in patients with neocortical or mesiotemporal epilepsy undergoing resective surgery showed that intravenous administration of 20 mg furosemide resulted in significant suppression of spontaneous epileptic spikes and electrical stimulation-evoked epileptiform discharges [51].

In a double-blind placebo-controlled trial in patients with partial epilepsy, adjunctive therapy with furosemide given orally at a dose of 40 mg/8 h for 4 weeks produced a significant reduction in the frequency of seizures [50]. In the same trial, a small increase in the serum concentration of concomitantly administered phenobarbital might have contributed to the improvement in patients randomized to furosemide.

An epidemiological study has demonstrated that in patients with arterial hypertension or congestive heart failure furosemide was associated with a decreased risk of developing unprovoked seizures [52]. However, odds ratios were not statistically significant when adjusting for matching variables.

Adverse effects

Furosemide may cause a variety of adverse effects, including dehydration, hypovolaemia, hyperglycaemia, hyperuricaemia, dizziness, paraesthesiae and arterial hypotension. Hypokalaemia may be accompanied by hypochloraemic alkalosis. Gastrointestinal symptoms have been described that may be attributed to hypokalaemia. Ototoxicity may occur acutely but is usually a transient phenomenon, although persistent tinnitus may develop.

Place in current therapy

Despite well-established experimental evidence of antiepileptic properties and some supporting clinical observations, furosemide does not, as yet, play a role in the treatment of epilepsy. It seems justified to consider furosemide at high doses in otherwise refractory status epilepticus, but adequate clinical data are currently lacking.

Ketamine

Ketamine is an analgesic and hypnotic drug that was first synthesized in 1962. Its current main use is in emergency and short-lasting procedures as an anaesthetic with strong analgesic and sedative effects. Ketamine has psychotropic effects and may

be abused, which is the reason why it has been illegal in the UK since 2006. Ketamine displays pronounced anticonvulsant properties in animal models of status epilepticus, and some case reports indicate that it may also be clinically effective in the treatment of status.

Chemistry

Ketamine is a chiral cyclohexanon derivative, and a racemate of the enantiomers (*S*)- and (*R*)-ketamine. The pharmacological profile of (*S*)-ketamine is qualitatively similar to the racemate, but the anaesthetic, analgesic and probably anticonvulsant potency of the (*S*)-enantiomer is three times that of the (*R*)-enantiomer and twice that of the racemate.

Mechanisms of action and activity in experimental models of seizures and epilepsy

The anticonvulsant properties of ketamine are assumed to be due to non-competitive antagonism to the *N*-methyl-D-aspartate (NMDA) receptor.

Experimental animal studies have demonstrated that ketamine suppresses epileptiform activity in advanced stages of status epilepticus *in vitro* [53] and *in vivo* [54–56]. Interestingly, such late seizure-suppressing effects are still seen after anticonvulsant drugs acting via enhancement of $GABA_A$ receptors have failed. The 'receptor-trafficking hypothesis' has been suggested to explain such effects [57]. Loss of efficacy of GABAergic agents after repetitive and serial seizures is assumed to be due to progressive decrease of $GABA_A$ receptors at the synaptic membrane. $GABA_A$ receptors are internalized into endocytotic vesicles and subsequently degraded [58]. In contrast, NMDA receptors are progressively transported to the synaptic membrane during ongoing epileptic activity, resulting in increasing numbers of functional excitatory NMDA receptors per synapse [59]. The latter is assumed to play an important role in rendering status epilepticus refractory to GABAergic drugs [60]. In this context, it is not surprising that ketamine co-administered with benzodiazepines in experimental studies has been demonstrated to have strong synergistic anticonvulsant effects [61].

Ketamine has an inhibitory effect on the peripheral reuptake of catecholamines such as noradrenaline and dopamine at the synaptic cleft. Potentiation of the pharmacological properties of endogenous and exogenous catecholamines has a stimulating effect on the cardiovascular system, which discriminates ketamine from all other anaesthetics, and via this property cardiodepressant effects of co-administered benzodiazepines may be neutralized.

Clinical pharmacokinetics

Since the sole indication for ketamine in epilepsy is, as yet, refractory status epilepticus, pharmacokinetic considerations in this chapter are restricted to intravenous administration. After bolus administration, the onset of action is seen within 30 s, and the elimination half-life is 2–3 h. The duration of action depends on the applied dose, and is approximately 5–15 min after 2 mg/kg and 12–25 min after 6 mg/kg.

The drug is extensively metabolized hepatically by the cytochrome P450 system to its active metabolite norketamine, which is excreted by the kidneys.

Drug interactions

Repetitive or continuous administration of ketamine results in enhanced propofol metabolism in rats [62], but the clinical relevance of this finding is unclear. Due to the vasopressor effects of ketamine, co-administration with thyroid hormones or sympathomimetic drugs may result in arterial hypertension or tachyarrhythmias.

Clinical efficacy

Ketamine may be an alternative anaesthetic drug in patients with status epilepticus refractory to other drugs. However, despite promising data from animal experiments and the availability of ketamine for decades, there are only very few publications on the clinical use of ketamine in status epilepticus. In a series of seven patients treated with ketamine for refractory status epilepticus, electrographic seizure control was reported in four patients on 0.3–5.8 mg/kg/h infusion for up to several days [63]. In other patients, a 7.5 mg/kg/h infusion was administered to terminate status epilepticus [64,65]. In five children aged between 4 and 7 years suffering from non-convulsive status epilepticus, oral administration of ketamine (1.5 mg/kg/day in two divided doses) for 5 days resulted in cessation of continuous epileptic activity in all cases [66].

Adverse effects

The main undesirable effects of ketamine are hallucinations, excitation and delirium due to the drug's psychotropic properties. Such effects can usually be avoided by co-administration of sedatives such as barbiturates, benzodiazepines or propofol. In a patient treated with ketamine for refractory status epilepticus, long-term follow-up revealed diffuse cerebellar and worsened cerebral atrophy [65]. This finding may not be specific and may well be the consequence of prolonged generalized status epilepticus itself. Other adverse effects of ketamine include hypertension and increased heart rate (though hypotension and bradycardia have also been reported), respiratory depression (at high doses), gastrointestinal disturbances, enhanced muscle tone manifested with tonic and clonic movements resembling epileptic seizures, and anaphylactic reactions.

Place in current therapy

In patients suffering from difficult-to-treat forms of status epilepticus, intravenous ketamine may be tried after failure of GABAergic anaesthetics. Improvement of haemodynamic conditions with ketamine infusion is an advantageous property compared with other catecholamine-requiring anaesthetics.

Lidocaine

The local anaesthetic and antiarrhythmic agent lidocaine was first synthesized in 1943 and marketed in 1948. Lidocaine has been reported to be effective in serial seizures and status epilepticus in children and adults.

Chemistry

Lidocaine [2-(diethylamino)-*N*-(2,6-dimethylphenyl)ethanamide] is an amino amide-type anaesthetic.

Mechanism of action

Lidocaine acts via inhibition of voltage-gated sodium channels during abnormal membrane depolarizations [67]. Therefore, the drug has membrane-stabilizing effects and probably inhibits fibre systems involved in direct cortical stimulation [68].

Clinical pharmacokinetics

Lidocaine is rapidly distributed into the brain and thus has an onset of action within minutes. The distribution half-life is 8–17 min and the elimination half-life is about 1.5–2 h. The drug is extensively metabolized in the liver by the enzyme CYP1A2 (and to a minor extent by CYP3A4) to metabolites which retain a pharmacological activity weaker than that of the parent drug.

Drug interactions

Enzyme-inducing agents such as phenobarbital or phenytoin may reduce the serum levels of lidocaine. The effects of lidocaine may be increased by beta-blockers. Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics (e.g. certain antiarrhythmics, such as mexiletine) since toxic effects are additive. Specific interaction studies with lidocaine and class III antiarrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised.

Clinical efficacy

Intravenous lidocaine has been reported to be effective in terminating 44% of cases of neonatal or infant convulsive status epilepticus after failure of conventional anticonvulsant treatment with diazepam, phenobarbital or phenytoin [69]. Lidocaine was bolus administered at 2 mg/kg, followed if necessary by infusion of 4 mg/kg/h for a mean of 14 h. Lidocaine seems to be useful in cases of status epilepticus attributable to acute medical conditions, such as convulsions with mild gastroenteritis [70]. In a randomized trial on 11 neonates with continuous and rapidly repeating seizures not terminated by phenobarbital, second-line treatment with lidocaine (4 mg/kg bolus, 2 mg/kg/h infusion) was successful in three out of five patients, while midazolam did not stop seizure activity in any of six patients [71].

Rare reports in adult status epilepticus described anticonvulsant effects of lidocaine either after failure of conventional AEDs including pentobarbital [72] or as a first-line agent in patients not treated with diazepam due to limited pulmonary reserve [73]. Lidocaine was bolus administered at 1–2 mg/kg followed by infusion rates of 1–4 mg/kg/h, a regimen that results in therapeutic plasma levels of 3–5 μg/mL [74]. In patients with intractable epilepsy, direct cortical administration of lidocaine during resective surgery resulted in marked reduction of spontaneous spike activity [75].

Adverse effects

The advantage of lidocaine in the treatment of status epilepticus lies in its lack of sedative effects and lack of depression of respiration at clinically relevant doses. Manifestations of CNS toxicity include confusion, drowsiness, tremulousness, tinnitus and psychosis. At serum concentrations >5 μg/mL the drug may have proconvulsant effects. Possible cardiovascular adverse effects include bradycardia, hypotension, arrhythmias and cardiovascular collapse, which may lead to cardiac arrest. Allergic reactions are characterized by skin rashes, oedema or, in the most severe instances, anaphylactic shock. Allergic reactions of the amide type are rare and may occur as a result of sensitivity either to the local anaesthetic agent or to other components in the formulation.

Place in current therapy

Lidocaine infusion may be administered in neonates and children with prolonged or repeated convulsions after failure of conventional anticonvulsants. The role of lidocaine in the management of adult refractory status epilepticus is less well defined, but the drug is also likely to be effective in this age group.

Mephenytoin

Mephenytoin has a hydantoin structure that resembles phenytoin and ethotoin. Its mechanisms of action are presumed to be similar to those of phenytoin. In animal models, its efficacy against pentylenetetrazole-induced seizures is greater. Mephenytoin inhibits post-tetanic potentiation and prevents the tonic phase in tonic–clonic seizures. It is also effective against seizures induced by bicuculline and picrotoxin [44].

Mephenytoin is stereoselectively converted to an active metabolite (nirvanol) and its metabolism is strongly influenced by the CYP2C19 genetic polymorphism.

Clinically, mephenytoin has the same spectrum of indications as phenytoin, but because of its common adverse effects its use should be limited to those patients unable to tolerate other drugs. Mephenytoin is effective against complex partial seizures and tonic–clonic attacks, but it may exacerbate absence seizures [44]. The usual daily dose is 300–600 mg in adults, given in divided doses.

Adverse effects include skin rashes, uncoordinated movements, sedation, hepatotoxicity, periarteritis nodosa and lupus erythematosus. Other adverse effects include psychotic reactions and behavioural disturbances.

Paraldehyde

Paraldehyde is a hypnotic that has been used primarily for the treatment of substance withdrawal seizures and status epilepticus. The mechanisms underlying its anticonvulsant action are unclear.

Paraldehyde is rapidly and almost completely absorbed and reaches a peak concentration in the plasma within 30–60 min after intramuscular administration and 1.5–2 h after rectal administration. About 30% is eliminated via the lungs and the remainder is metabolized in the liver [76]. The elimination half-life ranges from 5 to 8 h and can be greatly increased in hepatic disease.

Today, the sole indication for paraldehyde is in the treatment of acute seizures or status epilepticus. The literature concerning efficacy comprises case reports and small case series, and there are no modern assessments or controlled studies. It is apparent that paraldehyde is highly effective in stopping seizures, and although there are no controlled comparisons, paraldehyde prob-

ably has similar efficacy in acute seizures as benzodiazepines, barbiturates or phenytoin.

Paraldehyde has a small but useful place in contemporary therapy. It is mainly used as an alternative or sequel to the administration of diazepam in acute seizures or the stage of early status epilepticus [77,78]. It has the great advantage of little sedation or cardiorespiratory risk, and therefore it can be given rectally in situations where there are no facilities for resuscitation (e.g. at home or in residential institutions).

The usual rectal or intramuscular dosage is 5–10 mg (1 mg/mL) (adults) or 0.07–0.34 mg/kg (children). The drug should be diluted before rectal administration by mixing it with an equal volume of olive oil (or mineral oil). The dose can be repeated after 15–30 min. For intravenous use, according to Lockman [79], the drug is diluted with saline to a concentration of 10%, which is slowly infused at a dose of 0.3 mL/kg. In contemporary clinical practice, the intramuscular and the intravenous routes are rarely used because safer alternative routes of drug administration are available.

The main toxicity risks result from the use of inappropriately diluted or decomposed paraldehyde. Paraldehyde has a short shelf life, and to prevent decomposition, the drug should be freshly made and should not be unduly exposed to light. Paraldehyde solutions that have a yellowish colour may have deteriorated and should be discarded. The decomposed compound can result in precipitation, microembolism, thrombosis or cardiovascular collapse. The drug also reacts with rubber and plastic, therefore intravenous infusions must be given via glass sets and syringes. Paraldehyde has the advantage that arterial hypotension and respiratory arrest are less common than with benzodiazepines, phenytoin or barbiturates. Direct injury from arterial injection leading to both arterial and venous thrombosis has been reported [80]. Paraldehyde can also cause lactic acidosis. The intramuscular injection is extremely painful and can result in a sterile abscess and inflammatory response. Sciatic nerve damage is a risk if the injection is too close to the nerve.

Phenacemide

Phenacemide was introduced by Gibb *et al.* [81] for the treatment of refractory complex partial seizures. In animal models, the drug has been found to be effective in maximal electroshock-induced seizures and in increasing seizure threshold to pentylenetetrazole [82,83]. Clinically, a major problem of phenacemide is its tendency to induce personality disorders, aggression and acute psychosis [84]. Other adverse effects include sedation, insomnia, vertigo, headache and drowsiness. Because of its serious adverse effects, the drug is very rarely used today, although its efficacy may be greater and its toxicity less than previously thought [85]. Phenacemide is indicated only in intractable complex partial seizures when other drugs have failed. The total daily dose ranges from 20 to 40 mg/kg.

Propofol

Propofol is an intravenous anaesthetic which represents one of the therapeutic options in the management of status epilepticus refractory to benzodiazepines and phenytoin [86,87].

Chemistry

Propofol (2,6-diisopropylphenol) is a water-immiscible oil and is used as an emulsion of a soya oil–propofol mixture in water, which is why it appears as a highly opaque white fluid.

Mechanisms of action and activity in experimental models of seizures and epilepsy

Propofol has been shown to suppress epileptiform activity in experimental models *in vitro* and *in vivo* [88,89]. Propofol induces in neurones an inward hyperpolarizing current carried by chloride ions [90,91], through a mechanism of action that is different from that of barbiturates and benzodiazepines. Besides this direct effect on chloride channel conductance [91], propofol enhances $GABA_A$ receptor-mediated responses [92] and thus potentiates the effect of GABA on neurones [93–95]. Propofol also interacts with calcium channels and has a number of additional pharmacological effects, including decreased secretion of pro-inflammatory cytokines, modulation of the expression of nitric oxide, impairment of monocyte and neutrophil functions and potent radical scavenging activity [96].

Clinical pharmacokinetics

Propofol is highly protein bound (98%) and has a rapid onset of action within 2–4 min. The pharmacokinetic advantage of propofol is a short initial half-life of 30–60 min. As a result of this, however, clinical effects after bolus administration last only 4–8 min. Following a single bolus, propofol has no propensity to accumulate, while prolonged infusion may result in accumulation in fat tissue due to the high lipophilicity of the drug. Even after prolonged infusions (1–10 days), the decline in serum propofol concentration is initially relatively rapid, which may lead to awakening in a relatively short period when administration is discontinued. The terminal half-life, however, is quite long, in the order of 1–3 days after a 10-day infusion.

Propofol is metabolized mainly in the liver through the cytochrome P450 system and glucuronidation [96], and its plasma clearance is in the order of 1.6–3.4 L/min.

Drug interactions

Propofol is pharmacologically compatible with all other anticonvulsants used in status epilepticus, though additive effects on cardiopulmonary function have to be considered. Some opioids used in anaesthesiological practice may increase serum propofol concentrations, and propofol itself may increase the serum concentration of some opioids. Co-administration of ciclosporin with lipid emulsions such as in propofol may result in leucoencephalopathy.

Clinical efficacy

Propofol is administered in patients with generalized convulsive status epilepticus refractory to benzodiazepines and phenytoin [97]. Retrospective data have shown success rates of 67% with a median infusion rate of 4.8 mg/kg/h for a median of 3 days [98]. An uncontrolled prospective study has demonstrated termination of status epilepticus in 70% of patients, but propofol infusion rates had to be increased to a median maximum of 9.5 mg/kg/h to maintain an EEG burst–suppression pattern [99].

Adverse effects

Like other GABAergic anaesthetics, propofol has depressant effects on cardiopulmonary function. At doses administered for the treatment of refractory status epilepticus, mechanical ventilation is required. Arterial hypotension has to be treated with fluid resuscitation in all patients and up to 70% additionally require catecholamines [99].

Severe anaphylactic and anaphylactoid reactions may occur. The propofol infusion syndrome, which is characterized by cardiac failure, severe metabolic acidosis, rhabdomyolysis, hyperkalaemia and renal failure, is a severe and often fatal but rare complication, the risk of which increases with prolonged infusions >48 h at doses >4 mg/kg/h [100].

Place in current therapy

Propofol is one treatment option in those clinical forms of status epilepticus that require administration of anaesthetics after failure of first- and second-line anticonvulsants. In this condition, propofol is equally effective as barbiturates or midazolam, though the latter does not have the potency to induce an EEG burst–suppression pattern.

Trimethadione

Trimethadione was the first drug of choice for absence seizures until the introduction of ethosuximide and valproic acid. It was one of the first drugs that was shown to act selectively on a specific seizure type [101].

In animal models, trimethadione is more effective against pentylenetetrazole-induced seizures than against electrically induced seizures. Several mechanisms of action have been suggested, including augmentation of GABA [102], blocking of extracellular potassium accumulation [103] and induction of extracellular acidosis [104].

The drug is rapidly absorbed after oral administration and reaches a peak plasma concentration within 0.5–2 h. The half-life of trimethadione is about 16 h, but its active metabolite, dimethadione, has a half-life of about 10 days.

Trimethadione is highly teratogenic and must not be given to women of child-bearing age [105]. Adverse effects are dose related and include sedation and blurred vision [106], and skin reactions such as rash and erythema multiforme. Pancytopenia has been reported and a myasthenic syndrome may also occur [107].

The main indication for trimethadione is absence seizures that are not adequately controlled by other AEDs or in patients who do not tolerate these. Trimethadione is not effective in partial seizures or generalized tonic–clonic seizures. The usual daily dose is 20–40 mg/kg/day. The therapeutic plasma concentration of dimethadione ranges between 500 and 1200 μg/mL. Trimethadione is very rarely used today, and its production was discontinued in most countries by the end of 1994.

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59 Antiepileptic Drugs in Early Clinical Development

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Introduction

Seizure freedom with no adverse effects so as to enable the person with epilepsy to lead as normal a lifestyle as possible is the paramount treatment aim in epilepsy. This utopian ideal has not been realized by the generation of antiepileptic drugs (AEDs) licensed worldwide since 1989. Because the ideal treatment of many patients with intractable epilepsy still relies on the development of new AEDs, there is a substantial need for drugs with novel therapeutic targets that are more efficacious and which have improved adverse effect profiles and better pharmacokinetic characteristics. AEDs that improve the outcome of epilepsy and which prevent epileptogenesis and any secondary cerebral damage which may occur in epilepsy are needed. Drugs that could prevent the development of epilepsy following traumatic head injury, neurosurgical procedures and cerebrovascular accidents are very much needed, as well as AEDs that may prevent premature mortality, particularly due to sudden unexpected death, which often affects people with epilepsy.

In this chapter, various potential AEDs in early clinical development are reviewed in alphabetical order. These agents are summarized in terms of their mechanism of action, pharmacokinetic and interaction profiles, efficacy and adverse effect characteristics.

2-Deoxy-D-glucose

2-Deoxy-D-glucose, a chemical analogue of glucose that differs from normal glucose only by lacking a single oxygen atom at the 2 position, has been used for many years as a tracer in autoradiography and positron emission tomography imaging. 2-Deoxy-D-glucose is taken up into cells by normal glucose transport mechanisms, but unlike glucose cannot undergo metabolism and thereby acts as an inhibitor of glycolysis.

Mechanism of action

Inhibition of glycolysis results in an anticonvulsant action and it is through this mechanism that 2-deoxy-D-glucose is considered to act.

Activity in experimental models

2-Deoxy-D-glucose is effective in a variety of models, including seizures induced by pentylenetetrazole, maximal electroshock and pilocarpine, audiogenic seizures, kindled seizures and seizures induced in a corneal stimulation model [1].

Pharmacokinetics

2-Deoxy-D-glucose is rapidly absorbed and distributed after oral administration, with peak plasma concentrations occurring at 0.5–1 h and a half-life of 5–10 h [2]. As an analogue of glucose, 2-deoxy-D-glucose freely passes the blood–brain barrier and is delivered preferentially to brain regions in response to energy demand, specifically regions with circuitries generating seizures [3].

Drug interactions

The drug interaction profile of 2-deoxy-D-glucose is, at present, unknown.

Efficacy and adverse effects

The efficacy and tolerability profiles of 2-deoxy-D-glucose in patients with epilepsy are, at present, unknown.

Fluorofelbamate

Fluorofelbamate (2-phenyl-2-fluor-1,3-propanediol dicarbamate) is an analogue of felbamate, devoid of toxic metabolites, that has been designed to emulate the clinical efficacy of felbamate without its safety problems (potential to cause aplastic anaemia and liver toxicity) [4].

Mechanism of action

The exact mechanism of action of fluorofelbamate is unknown, but it appears to decrease responses to γ-aminobutyric acid (GABA), kainate and *N*-methyl-D-aspartate (NMDA) and to reduce voltage-dependent sodium currents [5].

Activity in experimental models

Fluorofelbamate has a greater potency than felbamate in a variety of models including seizures induced by picrotoxin and pentylenetetrazole, audiogenic seizures, kindled seizures and a self-sustaining status epilepticus model [5,6].

Pharmacokinetics

In male volunteers, fluorofelbamate is rapidly absorbed, with peak plasma concentrations (T_{max}) at 1.1 h, and exhibits linear pharmacokinetics. Its elimination half-life is ~16.7 h [5]. Although the exact metabolic pathways of fluorofelbamate are unknown, fluorofelbamate, unlike felbamate, is not metabolized to atropal-

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dehyde, the reactive aldehyde metabolite which is considered to be responsible for the rare but serious cases of felbamate-induced aplastic anaemia and liver toxicity [7].

Drug interactions
The drug interaction profile of fluorofelbamate is, at present, unknown.

Efficacy and adverse effects
The efficacy profile of fluorofelbamate is, at present, unknown. In male volunteers, single doses of fluorofelbamate up to 3 mg/kg were not associated with adverse events.

Ganaxolone

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), a neurosteroid that lacks classical hormonal activity, is a synthetic analogue of allopregnalone, a metabolite of progesterone [8]. It is a member of a novel class of neuroactive steroids called epalons, which allosterically modulate the $GABA_A$ receptor complex via a unique recognition site [9].

Mechanism of action
Ganaxolone is a potent positive modulator of $GABA_A$ receptors containing α1, α2 or α3 subunits, and does not show marked α-subunit selectivity [9].

Activity in experimental models
Ganaxolone is active in numerous seizure models, its profile being similar to other $GABA_A$ receptor modulators. It exhibits potent activity against seizures induced by pentylenetetrazole, bicuculline, aminophylline and corneal kindling, whilst it is less potent against maximal electroshock-induced seizures [9]. It is also effective against amygdala-kindled seizures [10] and various models of status epilepticus [11].

Pharmacokinetics
In healthy volunteers, ganaxolone, given in formulations containing a complex with cyclodextrin, was rapidly absorbed after oral ingestion, with peak plasma concentrations achieved within 1–3 h [12]. Peak plasma concentrations associated with a high-fat meal were three times higher than those achieved after intake with a high-carbohydrate meal, and nearly 12 times higher than those observed in fasted subjects. Plasma concentrations increased essentially dose-dependently (dose range 50–1500 mg) and subsequently declined biexponentially with a terminal half-life of 37–70 h. Plasma concentration versus time profiles after multiple doses of ganaxolone did not suggest any significant accumulation. There is no gender difference in respect to its pharmacokinetic characteristics [12]. Ganaxolone is highly bound (>99%) to plasma proteins and is metabolized, primarily by cytochrome P450 (CYP) enzymes CYP3A4/3A5, to yet unknown metabolites which are eliminated from plasma at a rate three to six times faster than the terminal half-life of ganaxolone [12].

Recently, several unique formulations of ganaxolone have been developed so as to address the variable absorption under different dietary conditions [13]. These include two solid capsule forms, one providing immediate release and the other providing pH-sensitive delayed release, and a new suspension form (50 mg/mL) for possible paediatric use. None of these formulations contains cyclodextrins. In healthy subjects the new suspension was associated with greater bioavailability in the fasted state and exposures after intake with food were comparable to those seen with the historical cyclodextrin complex. In the same studies, areas under the concentration–time curve (AUC) after intake with food were no more than two- to threefold greater than those observed after intake in the fasted state. Furthermore, the immediate-release capsule dosage form, in healthy volunteers, demonstrated comparable performance in the fed and fasted state to that of the new suspension, with a slightly prolonged T_{max} value. The delayed-release capsule is associated with a T_{max} of about 6 h and approximately one-half the exposure compared with the suspension or immediate-release capsules [13].

Drug interactions
Preliminary trials have not identified significant drug interactions with concomitant AEDs [12,14].

Efficacy
A non-randomized, non-blinded, open-label, dose-escalation trial of ganaxolone in paediatric patients (5–15 years) with refractory partial or generalized epilepsy reported that of the eight patients who completed the study, six responded to treatment and two were non-responders [15]. Three subjects entered the extension phase and one remained essentially seizure free for over 3.5 years. A double-blind, randomized, placebo-controlled study of ganaxolone (titrated up to a dose of 1875 mg/day) in 52 patients with refractory partial seizures preparing for surgical intervention, and whose concomitant AEDs were withdrawn, showed a strong trend in the ganaxolone patients towards a seizure reduction [16]. Overall, 50% of ganaxolone-treated patients compared with 25% of the placebo-treated patients completed the 8-day study period, and the unusually large survival rate in the placebo group probably reduced the response separation between the two groups. Ganaxolone has been reported to be effective in children with infantile spasms [17]. Of a total of 20 children with refractory infantile spasms, 16 completed an open-label study. Spasm frequency was reduced by at least 50% in 33% of subjects, with an additional 33% experiencing a 25–50% reduction.

Adverse effects
Adverse events reported in healthy volunteers given ganaxolone include sedation, dizziness, headache, gastrointestinal disturbances and fatigue. Interestingly, these were twice as common in females as in males, even though plasma ganaxolone concentrations were indistinguishable in the two genders [18]. In patients, treatment-emergent adverse events comprised a variety of central nervous system (CNS)-related effects, the most prominent being dizziness, somnolence, diarrhoea, nervousness and vomiting [14,15,18]. In adults with partial-onset seizures, the new suspension formulation at doses up to 500 mg three times a day, the highest dose regimen currently being tested, was well tolerated. Similarly, doses of up to 54 mg/kg/day (18 mg/kg three times a day) in 4- to 24-month-old infants with infantile spasms were well tolerated. A favourable tolerability profile was also obtained

in healthy volunteers with a 400-mg immediate-release solid dose form.

JZP-4

JZP-4 [3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine] is a structural analogue of lamotrigine, which resulted from a search for compounds with potentially improved pharmacokinetic and safety profiles compared with lamotrigine.

Mechanism of action

JZP-4 is a potent sodium ($Na_{v1.2a}$ and $Na_{v1.3}$) and high-voltage-activated calcium (types N, L and P/Q) channel blocker.

Activity in experimental models

JZP-4 appears to possess a broad spectrum of activity, in that it is effective in a variety of seizure models including the mouse and rat maximal electroshock models of generalized tonic–clonic seizures; the epilepsy-like (El) mouse model, which is predictive of efficacy in partial seizures; the rat hippocampal- and amygdala-kindling models; and the mouse 6-Hz model [19].

Pharmacokinetics

In healthy volunteers, orally administered JZP-4 was rapidly absorbed and eliminated primarily by metabolism. Excretion of JZP-4 in urine is low, with less than 0.1% of the administered dose recovered in urine as unchanged JZP-4.

Drug interactions

In vitro studies show that JZP-4 has no inhibitory effect on CYP2E1 and a weak inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Additionally, JZP-4 had no significant inhibitory effect on UDP-glucuronosyltransferase (UGT) enzymes UGT1A1, UGT1A4 or UGT1A9 and minimal effect on UGT1A6, UGT2B7 and UGT2B15. JZP-4 did not induce CYP1A2 or CYP3A in isolated human hepatocytes [19].

In healthy volunteers, the apparent oral clearance of a single dose of JZP-4 was reduced by approximately 50% during co-administration with an oral contraceptive (Necon® 1/35 for one cycle), and increased approximately twofold during co-administration with carbamazepine (up to 600 mg/day for 17 days). Co-administration with valproic acid (500 mg twice daily for 10 days) did not result in a clinically significant change in JZP-4 pharmacokinetics [13].

Efficacy and adverse effects

The efficacy and tolerability profiles of JZP-4 are, at present, unknown.

Safinamide

Safinamide (FCE 26743; PNU-151774E; NW-1015) was developed based on the observation that milacemide, a compound no longer in development, possesses weak anticonvulsant activity combined with monoamine oxidase (MAO)-A and -B inhibitory activity. Safinamide is expected to have greater anticonvulsant activity than milacemide [20–23]. Its clinical development programme, however, is currently focused on the treatment of Parkinson's disease [24].

Mechanism of action

Safinamide, which chemically corresponds to (*S*)-(+)-2-[4-(3-fluorobenzyloxy)benzylamino]propanamide, methansulfonate, acts via an action on site 2 of the sodium channel. It is also said to modulate calcium currents and to inhibit MAO-B activity [20,21].

Activity in experimental models

Safinamide is effective in a variety of seizure models (bicuculline, picrotoxin, 3-methyl-aspartate, strychnine, NMDA and electrically induced seizures), in which it acts by preventing seizure spread [22,23]. In these models, safinamide is associated with a very high therapeutic index, suggesting minimal toxicity. In the kainic acid model, safinamide protects against both the seizures and the ensuing neuronal damage [23].

Pharmacokinetics

In healthy volunteers, safinamide is rapidly absorbed, with peak concentrations occurring within 2 h of oral ingestion. A high-fat meal delays absorption without affecting the extent of absorption. Safinamide is 92% bound to plasma proteins. Plasma safinamide concentrations increase linearly with dose and the elimination half-life is 21–23 h.

Drug interactions

In vitro studies suggest that safinamide has no inducing or inhibiting activity on the different CYP isoenzymes that are known to be involved in the metabolism of other AEDs. Nevertheless, plasma safinamide concentrations have been reported to be decreased in patients co-prescribed with enzyme-inducing AEDs such as carbamazepine and phenobarbital [24].

Efficacy

In a phase II open-label trial of safinamide as add-on treatment for uncontrolled epilepsy (different seizure types), 41% of 38 subjects obtained >50% seizure reduction during a 12-week escalating dose period (up to 300 mg/day) compared with baseline [24].

Adverse effects

Overall, safinamide was well tolerated in the trial described above. The most common treatment-emergent adverse events included dizziness, vertigo, nausea and transient visual disturbance, all of which were judged as mild to moderate in nature.

Seletracetam

Seletracetam (ucb 44212) is an analogue of levetiracetam.

Mechanism of action

Seletracetam's chemical structure corresponds to that of levetiracetam with a substitution at the 4-position on the

2-pyrrolidinone ring [25]. Seletracetam binds selectively, stereospecifically and with high affinity (10-fold greater that that of levetiracetam) to synaptic vesicle protein 2A (SV2A), which is thought to be involved in synaptic vesicle exocytosis and neurotransmitter release [26].

Activity in experimental models

Seletracetam, like levetiracetam, is inactive in maximal electroshock and pentylenetetrazole seizure models. However, it is 10-fold and 25-fold more potent than levetiracetam in the corneal kindling and in the Genetic Absence Epilepsy Rat of Strasbourg (GAERS) models [27]. It is also effective in the genetically sound-susceptible mouse model.

Pharmacokinetics

Seletracetam is rapidly absorbed, with a T_{max} of <1 h, and has linear pharmacokinetics. Its volume of distribution is 0.6 L/kg. Seletracetam is minimally bound (<10%) to plasma proteins [28]. Ingestion with a high-fat meal delays the rate of absorption (median T_{max} delayed from 0.5 to 4 h) and results in a 39% reduction in the maximum seletracetam concentration achieved, but had no effect on overall extent of absorption [29]. Seletracetam is eliminated by hydrolysis and excretion in urine, with a total apparent clearance of approximately 0.8 mL/min/kg. Its primary metabolite is an acidic inactive metabolite (ucb-101596-1), the concentration of which in plasma is approximately 10-fold lower than that of the parent compound. Two additional minor metabolites have been identified in urine. Overall, 25% of a seletracetam dose is excreted in the unchanged form [28]. In young healthy subjects, the half-life of seletracetam is about 8 h.

Drug interactions

Based on *in vitro* data, there is a low potential for interactions involving seletracetam. The drug interaction profile of seletracetam in the clinical setting is, at present, unknown.

Efficacy

In a placebo-controlled study of patients with photosensitive epilepsy, seletracetam was markedly effective in reducing the photo-paroxysmal EEG response [30].

Adverse effects

In healthy volunteer studies, seletracetam was well tolerated following both single (200–600 mg) and multiple oral doses (200 mg two times a day) [28,29,31]. The most frequently observed adverse events, which were considered to be mild to moderate and resolved without medical intervention, included somnolence, dizziness, euphoria and nausea.

T2000

T2000 (1,3-dimetoxymethyl-5,5-diphenylbarbituric acid) is a prodrug which is rapidly metabolized to monomethoxymethyl-5,5-diphenylbarbituric acid (MMMDPB) and 5,5-diphenylbarbituric acid [32]. Its current clinical development focuses on its potential usefulness in the treatment of essential tremor rather than epilepsy [13].

Mechanism of action

The mechanisms of action of 5,5-diphenylbarbituric acid, the metabolite best characterized pharmacologically, resemble those of both phenytoin and barbiturates. It suppresses high-frequency repetitive neuronal discharges in cat motor nerve terminals in a manner similar to that of phenytoin, whereas it depresses synaptic discharges in the cat spinal cord in a manner similar to that of phenobarbital [33]. Furthermore, it enhances slow outward current and suppresses repetitive firing in *Aplysia* giant neurones with similar efficacy to and higher potency than phenobarbital [34].

Activity in experimental models

5,5-Diphenylbarbituric acid is effective in the pentylenetetrazole and maximal electroshock tests in mice and rats, decreases the development of pentylenetetrazole-induced kindled seizures in mice and exhibits antiepileptogenic properties in kindled seizures induced by repeated administrations of low doses of cocaine in mice [13].

Pharmacokinetics

Because food enhances the absorption of T2000, the compound is usually ingested with food [35]. In healthy subjects, the pharmacokinetics of T2000 and its primary metabolites 5,5-diphenylbarbituric acid and MMMDPB show near-linearity up to 1200 mg/day dosing [32], with steady-state concentrations achieved within 2 weeks. Plasma protein binding values for T2000, 5,5-diphenylbarbituric acid and MMMDPB are 67%, 35% and 51%, respectively [36], and mean terminal half-lives are in the range of 9–29 h, 27–65 h and 8–27 h, respectively. T2000, 5,5-diphenylbarbituric acid and MMMDPB are further metabolized via hydroxylation and form glucuronide conjugates that are eliminated in urine [32,37]. Diphenylbarbituric acid, MMMDPB, and hydroxy-MMMDPB are formed by CYP2C19, while hydroxy-diphenylbarbituric acid is formed primarily by CYP2C9.

Drug interactions

In vitro studies using human liver microsomes indicate that MMMDPB is a competitive inhibitor of CYP2C19 and CYP2C9 and that 5,5-diphenylbarbituric acid is a competitive inhibitor of CYP2C9 and CYP3A4 [38]. Additionally, 5,5-diphenylbarbituric acid and MMMDPB are potent inducers of CYP3A4 [38].

Efficacy and adverse effects

The efficacy and tolerability profiles of T2000 are, at present, unknown.

Talampanel

Talampanel (LY300164; GIKY 53773) is structurally similar to conventional 1,4-benzodiazepines, but it does not share the same pharmacology and does not interact at the benzodiazepine–GABA receptor complex.

Mechanism of action

Talampanel, which corresponds chemically to (*R*)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo(4,5-

H)(2,3)benzodiazepine, is probably a non-competitive antagonist at the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptor subtype of glutamate [28]. It seems to act not directly on the AMPA receptor, but at an allosteric site referred to as the GYKI receptor [39].

Activity in experimental models

Talampanel shows a broad spectrum of anticonvulsant activity in animal models, including maximal electroshock- and pentylenetetrazole-induced seizures in mice, chemically and electrically kindled seizures in mice, and a mouse model of phenytoin-resistant status epilepticus. In addition, talampanel enhances the anticonvulsant effects, in various seizure models, of numerous AEDs including phenytoin, phenobarbital, valproic acid and clonazepam [40–42].

Pharmacokinetics

After oral ingestion, talampanel is rapidly absorbed, with peak plasma concentrations occurring within 1–3 h [43]. A high-fat or high-caloric meal delays the absorption of talampanel, with T_{max} values ranging from 1.9 to 2.4 h. Binding to plasma proteins is of the order of 75% (range 67–88%). The elimination of talampanel is probably via a combination of first-order and capacity-limited processes. Its elimination half-life in healthy volunteers is about 4 h. Although its metabolic pathways have not been completely characterized in man, acetylation appears to occur whereby talampanel is converted to *N*-acetyl-talampanel by hepatic *N*-acetyltransferase 2 [44]. This metabolic route is not major but there appears to be significant inter-patient differences in plasma concentrations of *N*-acetyl-talampanel, which is pharmacologically active, and may also contribute to adverse effects in some patients.

Drug interactions

Talampanel has been shown in an *in vitro* setting to be an irreversible inhibitor of CYP3A and consequently it would be anticipated that it may inhibit the metabolism of CYP3A substrates such as carbamazepine. Indeed, carbamazepine plasma concentrations are elevated during carbamazepine and talampanel co-administration. Also, there is evidence to suggest that talampanel inhibits valproic acid metabolism, resulting in increased plasma valproic acid concentrations [43]. In patients with epilepsy, the clearance of talampanel is enhanced by enzyme-inducing AEDs such as carbamazepine and phenytoin, so that its half-life is reduced to about 3 h, whilst valproic acid does not appear to affect talampanel clearance [43,45,46].

Efficacy

A double-blind, placebo-controlled, cross-over study evaluated talampanel in 49 patients with refractory partial seizures. Three target talampanel doses were chosen (up to 75 mg three times a day in patients co-medicated with enzyme-inducing AEDs, up to 60 mg three times a day in patients co-medicated with enzyme-inducing AEDs plus valproate and in patients not receiving enzyme-inducing AEDs or valproate, and up to 25 mg three times a day in patients receiving valproate without enzyme inducers). Compared with placebo, talampanel was associated with a 21% reduction in median seizure frequency [47]. An interim analysis of the open-label arm of 100 patients who participated in an earlier randomized double-blind, placebo-controlled, multicentre study showed responder rates (≥50% seizure reduction from baseline) of 39.6% for simple partial seizures, 33.8% for complex partial seizures and 32.3% for partial seizures with secondary generalization [48].

Adverse effects

In healthy male volunteers, who received either a single 100 mg dose or multiple doses (20–50 mg three times a day) of talampanel, the drug was well tolerated [49]. Adverse events included mild drowsiness, dizziness, ataxia and paraesthesiae and occurred at doses above 50 mg [45]. In patients with epilepsy, the most significant adverse events have been dizziness, ataxia, headache and somnolence [37,43,48].

Tonabersat

Tonabersat (SB-220453) is a chiral novel benzoylaminobenzopyran compound that has a similar structure to carabersat (SB-20469), a potential AED no longer in clinical development. Its current clinical development focuses on its potential usefulness in migraine, rather than epilepsy [13].

Mechanism of action

Tonabersat [(3S-cis)-*N*-(6-acetyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)-3-chloro-4-fluorobenzamide] represents a 'first-in-class' neurotherapeutic agent that does not act via any established anticonvulsant mechanism. Instead, tonabersat selectively and specifically binds to a unique stereoselective site in the CNS, thought to be at the neuronal gap junction, and its potency as a gap junction blocker is two- to threefold greater than that of carabersat [50].

Activity in experimental models

Tonabersat increases the threshold for electrically induced seizures in mice and rats and is also active against pentylenetetrazole-induced seizures, inhibiting tonic but not myoclonic seizures [13].

Pharmacokinetics

After oral ingestion of a single dose (2–80 mg), tonabersat is rapidly absorbed with a median T_{max} of 0.5–3 h. Absorption is delayed by a high-fat meal (T_{max} is extended by approximately 3 h) but food has no effect on the extent of absorption. Peak plasma concentrations were generally dose proportional between 2 mg and 40 mg. Tonabersat is highly bound to plasma proteins (98.2%) and undergoes metabolism by cytosolic carbonyl reductase enzymes to a reduced ketone, with negligible amounts excreted in urine unchanged. The primary metabolite is detectable in plasma. Acetyl hydroxylation via the CYP3A family of enzymes accounts for a minor hydroxyl metabolite. Tonabersat plasma concentrations decline in a biexponential manner with mean terminal half-life values of 24–40 h [13].

Drug interactions

Co-administration of the oral contraceptive Microgynon® (active ingredients ethinylestradiol and levonorgestrel) with 80 mg tona-

bersat for 7 days (days 4 to 10 of the menstrual cycle), resulted in an increase in peak plasma ethinylestradiol concentration by a mean of 14% [90% confidence interval (CI) 1.0–28.0%] and of ethinylestradiol AUC by a mean of 21% (90% CI 1.3–30.0%). However, tonabersat had no effect on the metabolism of levonorgestrel.

Sumatriptan and tonabersat co-administration in healthy subjects resulted in no significant effects of either drug on the pharmacokinetic profile of the other [13].

Efficacy and adverse effects

The efficacy profile of tonabersat in patients with epilepsy is, at present, unknown.

Tonabersat has been administered to more than 1000 subjects (both healthy subjects and migraine patients), either as single oral doses (up to 80 mg) or as repeated doses (up to 80 mg/day for up to 7 days). Overall, the drug was well tolerated, with headache, nausea, dizziness and somnolence being the most commonly reported adverse events, the majority of which were mild or moderate and rapidly resolved [13].

Valrocemide

Valrocemide (*N*-valproyl-glycinamide; TV 1901) is a valproyl derivative of glycine.

Mechanism of action

The mechanism of action of valrocemide is unknown. An effect on GABA or glutamate-sensitive ion channels has been ruled out.

Activity in experimental models

Valrocemide exhibits broad-spectrum anticonvulsant activity in numerous seizure models including maximal electroshock, pentylenetetrazole, picrotoxin and bicuculline-induced seizures as well as sound-induced seizures in Frings mice, and hippocampal-kindled seizures and focal seizures from corneal-kindled rats [51].

Pharmacokinetics

In healthy volunteers, valrocemide is rapidly absorbed and exhibits linear pharmacokinetics after single oral doses ranging between 250 and 4000 mg and multiple doses ranging between 250 and 1000 mg three times a day [52]. The plasma protein binding of valrocemide is <25%. Its elimination half-life is 6.4–9.4 h after single-dose administration and 7.2–8.5 h after multiple-dose administration. Oral clearance is 5–7 L/h. Approximately 10–20% of an administered dose is excreted unchanged in urine, and 40% is excreted in the form of valproyl glycine. Urinary valproic acid accounts for 4–6% of an administered valrocemide dose.

Drug interactions

In vitro studies using CYP isoenzymes indicate that significant drug interactions with other AEDs would not be anticipated. Nevertheless, in a series of 22 patients with epilepsy receiving concomitant AEDs, higher valrocemide clearance and shorter valrocemide half-life values were observed in patients receiving enzyme-inducing AEDs. In contrast, valrocemide clearance and half-life in patients not on enzyme-inducing AEDs were similar to those recorded in healthy volunteers [53].

Efficacy

Using an open-label study design during a 13-week period, the efficacy of valrocemide has been investigated in 22 patients with epilepsy. Valrocemide was associated with reduced seizure frequency in 15 patients, two of whom became seizure free [53].

Adverse effects

In preliminary open-label adjunctive therapy studies in patients with epilepsy, whereby valrocemide was administered at doses up to 2000 mg two times a day, no serious treatment-emergent adverse events were recorded. Most adverse events reported were mild to moderate and were CNS or gastrointestinal tract related [53].

YKP3089

YKP3089 is a novel compound with broad-spectrum anticonvulsant activity.

Mechanism of action

The mechanism of action of YKP3089 is, at present, unknown.

Activity in experimental models

YKP3089 is effective in a broad range of models including maximal electroshock-induced seizures in mice and rats, pentylenetetrazole- and picrotoxin-induced seizures, the hippocampal-kindled rat, the mouse 6-Hz model and the rat lithium–pilocarpine-induced intractable seizures model [53].

Pharmacokinetics

In healthy volunteers, YKP3089 shows linear pharmacokinetics over a large dose range (5–750 mg), with a median T_{max} of 1.5–3.5 h. Co-ingestion with a high-fat meal had no significant effect on the pharmacokinetics of YKP3089. Its mean volume of distribution (V_d/F) was 37–55 L, with a mean apparent oral clearance of 0.63 L/h and a half-life of 30–75 h. Dose linearity was also observed in a multiple-dose 14-day study with once-daily dosing, whereby both peak plasma concentrations and AUC increased linearly [13].

Drug interactions

The interaction profile of YKP3089 is, at present, unknown.

Efficacy and adverse effects

The efficacy profile of YKP3089 is, at present, unknown. YKP3089 was well tolerated in healthy volunteers, the most common adverse events being CNS related. Adverse events were of mild to moderate intensity and resolved rapidly.

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Section 4
Presurgical Assessment and Epilepsy Surgery

The Treatment of Epilepsy, Third Edition Edited by S. Shorvon, E. Perucca and J. Engel
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60 Overview of Surgical Treatment for Epilepsy

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Introduction

Epilepsy is one of the most serious primary disorders of the brain, accounting for 1% of the global burden of disease [1]. Pharmacotherapy is unsuccessful in controlling seizures in 30–40% of patients [2], and 80% of the cost of epilepsy in the industrialized world is accounted for by patients with medically intractable seizures [3]. It is estimated that four million people worldwide with pharmacoresistant epilepsy might be candidates for a surgical procedure that could stop disabling seizures in 60–80%. However, only slightly more than 8000 therapeutic surgical procedures were performed for epilepsy between 1986 and 1990, the last time a worldwide survey was performed [4]. There is little evidence that this number has increased substantially in recent years. Surgical treatment for epilepsy is arguably the most underutilized of all accepted therapeutic interventions in the entire field of medicine. Furthermore, when patients *are* referred for surgery, there is an average duration of 22 years between the onset of epilepsy and referral [5]. Therefore, not only do most surgical candidates never get referred for surgery, but those who do usually receive it too late to prevent or reverse disabling psychological and social consequences of recurrent seizures [6]. In theory, for many of these patients, early surgical intervention could prevent a lifetime of disability.

It is understandable that surgical treatment has not been considered feasible in the developing world, where most people with epilepsy live; however, on the positive side, tremendous advances have been made in recent years to establish epilepsy surgery programmes in several developing countries (see Chapter 85). Given this, it is unclear why epilepsy surgery remains so underutilized in virtually all industrialized countries in view of continuing advances in the safety and efficacy of surgical treatment, the numerous books that have been published on this subject [7–27] and the uncontested cost-effectiveness of surgical treatment, which must be contrasted not only with the monetary cost of a lifetime of disability, but also with the human cost of premature death [28,29], morbidity [30] and social and psychological compromise [31–33]. One often stated reason in the past, confirmed by a US National Institutes of Health (NIH) Consensus Panel in 1990 [34], was the absence of a randomized controlled trial (RCT), the 'gold standard' needed to demonstrate the superiority of surgical intervention over continued pharmacotherapy. In 2001, however, an RCT carried out at the University of Western Ontario on patients with long-standing temporal lobe epilepsy (TLE) found that 64% of patients were free of disabling seizures 1 year after surgery, compared with only 8% after continued drug trials [35,36]. As a result of this study and a meta-analysis of 24 surgical series published between 1990 and 2000, a practice parameter was issued by the American Academy of Neurology (AAN), in collaboration with the American Epilepsy Society and the American Association of Neurological Surgeons, concluding that surgery is the treatment of choice for medically intractable TLE [37]. It is important here to note that the conclusion of the practice parameter would not have been permitted by the AAN, according to their current standards of evidence-based medicine, on the basis of published uncontrolled surgical series alone, due to the belief that the results of such series can be biased. The AAN accepted this conclusion only because of the RCT. Interestingly, the figure of two-thirds of operated patients free of disabling seizures in the RCT was exactly the same as the average for the practice parameter meta-analysis and the data presented at the 1992 Palm Desert Conference on Treatment of the Epilepsies [38], indicating that bias was not a significant factor in uncontrolled reports.

There are many other types of surgery performed for epileptic seizures due to conditions other than TLE, as discussed later in this chapter, and in the rest of this section, and there is, therefore, no reason to believe that the successful outcomes reported by published series of these surgical procedures are any less valid than those reported for TLE, even though RCTs have not been performed.

The AAN practice parameter recommended early surgical intervention for TLE in order to avoid irreversible adverse psychological and social consequences, as well as significant morbidity and mortality in some populations; however, there are insufficient data to provide definitive guidelines on when to refer patients for surgical treatment. Although it is essential to more effectively disseminate information to primary care physicians, general neurologists and patients about the proper role of surgery in the armamentarium of therapy for epilepsy, there remains a need to collect many more data about the natural history of surgically remediable epilepsies, such as TLE, after failure of a few appropriate drug trials. Identification of reliable risk factors for continued pharmacoresistance would permit establishment of rational guidelines to dissuade physicians and patients alike from trying yet another drug when disabling epileptic seizures are seriously disrupting school, work or interpersonal relations. It is clear that extensive documentation of the safety and efficacy of epilepsy surgery has been insufficient to alter the standard of practice in the community, and that convincing data are now needed to permit reliable identification of patients who will continue to

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experience psychological and social deterioration, and increased risk of morbidity and mortality, as a result of persistent seizures, if surgical intervention is to be performed in a timely fashion in the future.

Historical perspective

The development of the modern era of epilepsy surgery paralleled the development of concepts of localization of function within the brain, and the field of neuroscience [39]. Beginning in the mid-nineteenth century, studies on patients with focal epilepsy provided seminal insights into the location of functions within the human cortex and, conversely, this information led directly to the localization of surgically resectable epileptogenic lesions that were not readily visible on routine examination.

At the turn of the 19th century, popular interest in phrenology, a misguided belief that personality types could be diagnosed by palpation of bumps on the head believed to reflect various localized brain functions [40], was so vehemently rejected by the scientific community of the time that half a century passed before neuroscientists were willing to take localization of brain function seriously. The British philosopher Herbert Spencer [41] returned respectability to this area of investigation by stating, in 1855, that 'localization of function is the law of all organizations whatever: separation of duty is universally accompanied by separateness of structure; and it would be marvelous were an exception to exist in the cerebral hemispheres'. Spencer had a profound influence on John Hughlings Jackson, who mapped human cortical functions by observing patients with focal seizures and correlating initial ictal semiology with pathological abnormalities identified at autopsy [42]. Jackson, who was appointed consultant at London's National Hospital for the Paralysed and Epileptic at Queen Square in 1862, is credited with recognizing focal seizures of cortical origin as epilepsy, at a time when most physicians were concerned only with generalized tonic–clonic convulsions, which they believed originated in the medulla oblongata. Although Pritchard [43], Bright [44] and Todd [45] in Britain, Bravais [46] in France and Griesinger [47] in Germany had previously described ictal and postictal focal phenomena, Jackson's clinical–pathological correlations established the cortex as the origin of focal seizures, which ultimately developed into an approach for localizing epileptogenic regions for surgical resection. His theories were tested by his colleague David Ferrier [48], an electrophysiologist who reproduced the ictal behaviours described by Jackson with faradic stimulation of appropriate areas of monkey cortex. In 1886, Victor Horsley performed three successful surgical resections for epilepsy by removing lesions that were 'invisible' preoperatively, but predicted by seizure semiology, and published this the same year [49]. Of note is that Jackson and Ferrier were also present in the operating theatre for the first surgery, constituting the team of neurologist, electrophysiologist and neurosurgeon that is still essential for the surgical treatment of epilepsy today.

Although the modern era of epilepsy surgery is traditionally considered to begin with the 1886 paper by Horsley, he was not the first to successfully remove epileptogenic brain tissue. The first publication was probably that of Benjamin Winslow Dudley [50], who reported on five patients operated on between 1808 and 1818 at Transylvania University in Lexington, Kentucky, USA. Three became seizure free and the other two had marked improvement. Survival alone was remarkable prior to the common use of antiseptic and anaesthetic techniques, and Dudley commented that his results would not have been possible in an unhealthy urban environment. The Scottish neurosurgeon William Macewen predated Horsley with a series of publications [51–53] describing a number of successful surgical interventions for epilepsy, many of which involved removal of 'invisible' lesions identified solely on the basis of Jackson's clinical–pathological correlations. Bennett and Godlee [54] in England and Durante [55] in Italy also performed surgery prior to Horsley; however, it was Horsley's publication that stimulated interest in surgical treatment for epilepsy in carefully selected patients. Germany was particularly active, with Feodor Krause [56] and Otfrid Foerster [57] being the most prominent epilepsy neurosurgeons in the early 20th century, but it was Foerster's pupil, Wilder Penfield, who subsequently founded the Montreal Neurologic Institute and set the standards for surgical treatment of epilepsy for decades to come.

Early surgical therapy for epilepsy was lesion directed, and only patients with visually apparent structural abnormalities of neocortex were considered surgical candidates. Lesions were localized directly by skull deformities, or indirectly by neurological exam and ictal semiology, then defined intraoperatively, until the development of pneumoencephalography in 1919 [58] and cerebral angiography in 1934 [59]. Confirmation of epileptogenic tissue was usually obtained by faradic stimulation of cortex at surgery. Penfield and Jasper also used this technique to map the human motor and sensory homunculus [60]. Although most surgical procedures involved localized cortical resection, a variety of other surgical approaches were attempted during the first half of the 20th century, including corpus callosotomy, first performed by van Wagenen and Herren in the USA in 1940 [61], and hemispherectomy, first performed by McKenzie in 1938 in Canada [62] and expanded upon by Krynauw in South Africa in 1950 [63].

The field of epilepsy surgery was radically changed with the advent of electroencephalography (EEG) and its application to epilepsy diagnosis, most importantly by Gibbs, Gibbs and Lennox [64] in the USA and Jasper and Kershman [65] in Canada. The latter were the first to recognize that temporal lobe EEG spikes were characteristic of what had been referred to as psychomotor seizures, and Bailey and Gibbs [66] were the first to report a series of temporal lobe corticectomies, based on EEG evidence alone. In the same year, however, Jasper and colleagues [67] provided detailed descriptions of the scalp and intraoperative EEG findings, including a seizure originating in mesial temporal structure, on a larger series of patients who had undergone temporal corticectomies, reported by Penfield and Flanigin [68] a year earlier. Following these reports, centres all over the world began performing temporal lobe resections for psychomotor seizures, and a new era of epilepsy surgery had begun. Subsequent important developments included recognition that mesial temporal structures needed to be resected [69], the development of chronic intracranial recording [70,71], EEG telemetry [72] and *en bloc* resection of mesial temporal structures [73], which ultimately led to the recognition of hippocampal sclerosis [74] as the most common lesion in what has now come to be known as mesial temporal lobe epilepsy (MTLE).

For several decades, interictal and ictal EEG abnormalities derived from scalp recordings, depth and subdural electrodes, and intraoperative electrocorticography, provided the most important localizing information for epilepsy surgery, but additional important confirmatory evidence was provided by a number of other approaches, including neuropsychological evaluation [75], including the intracarotid amytal test [76], until the advent of modern neuroimaging in the late 1970s. The first, X-ray computed tomography (CT), identified relatively large structural lesions, but not hippocampal sclerosis [77]. Next, positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) identified mesial temporal hypometabolism in a large percentage of patients with TLE [78,79] and children with cortical dysplasia [80]. Then, ictal single-photon emission computed tomography (SPECT) revealed areas of hyperperfusion that often delineated the epileptogenic region [81]. Later, the development of high-resolution magnetic resonance imaging (MRI) not only revealed various structural lesions that could be seen on CT, but also delineated hippocampal sclerosis [82] and areas of cortical dysplasia [83] in patients who previously would have been diagnosed with non-lesional, cryptogenic epilepsy. With this development, the field of epilepsy surgery has, for the most part, returned back to its lesion-directed roots, with electrophysiology providing essential confirmatory evidence that the lesion is epileptogenic. Localization of so-called non-lesional, or cryptogenic, focal epilepsies, as well as epilepsies associated with diffuse or multifocal lesions in which only a small area generates the habitual seizures, must still be based primarily on electrophysiological, usually invasive, investigations, and these conditions remain a major frontier for future research. There continue to be rapid developments, however, in both structural and functional neuroimaging that undoubtedly will contribute importantly to facilitation of presurgical evaluation, and the cost-effective identification of greater numbers of surgical candidates in the future, as well as improved safety and efficacy of surgical intervention.

Epileptic disorders

The International League Against Epilepsy (ILAE) has defined epilepsy as 'a chronic disorder of the brain characterized by an enduring propensity to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one seizure' [84]. Although the ILAE is in the process of reviewing the definition and classification of epilepsy syndromes [85], according to the 1989 International Classification [86], which remains in effect, the underlying predisposition may be idiopathic (primary) or symptomatic (secondary). At the present time, only symptomatic epilepsies are treated surgically.

The progressive nature of epilepsy

Whereas idiopathic epilepsies are largely benign and seizures often remit in adolescence or early adulthood, some symptomatic epilepsies exhibit progression; epileptic seizures can become more frequent and/or more severe, and disabling interictal behavioural disturbances can appear. Early surgical intervention is particularly important when progressive features of an epileptic condition are present. Symptomatic epilepsies due to diffuse bilateral brain damage are usually associated with generalized seizures, as well as developmental delay and mental retardation, which, to a large extent, can be attributed to the underlying pathophysiological substrate. The complex partial seizures of mesial temporal lobe epilepsy (MTLE) [87–89] often become pharmacoresistant [90]. In this situation, the appearance of certain disabling interictal behavioural disturbances can be directly attributed to psychological and social causes; however, there is also evidence that other disturbances, and also worsening of seizures, and even structural changes, can reflect direct progression of the epileptogenic process [91,92]. Phenomena described in experimental animal models, such as kindling [93] and the mirror focus phenomenon [94], provide indisputable evidence of secondary epileptogenesis, whereby repeated epileptic discharges give rise to additional distant areas of epileptogenicity and enduring disruption of normal function. Furthermore, chronic epileptic activity induces natural homeostatic seizure-suppressing mechanisms that act to terminate ictal events, prevent their generation, and limit their spread. These protective influences account for some postictal deficits and undoubtedly have a more persistent effect on normal neuronal function, perhaps contributing to the occurrence of interictal behavioural disturbances [91]. There is also evidence to support concern that frequent seizures or epileptiform discharges can interfere with normal growth and development of the immature brain [95], and contribute directly to progressive memory disturbances that, in some cases, can be irreversible [96].

Clinical evidence supports the detrimental effect of continuing seizures on subsequent ictal manifestations and interictal behaviour. For instance, outcome after surgical resection for TLE and neocortical epilepsy appears to be better when the interval between the onset of seizures and surgical intervention is short [97]; surgical resection of a localized area of cortical dysplasia in infants and small children with infantile spasms can not only eliminate spontaneous seizures, but also reverse developmental delay [98]; and anterior temporal lobectomy, which is successful in abolishing spontaneous seizures, improves memory function of the contralateral temporal lobe, and commonly increases intelligence [99].

The concept of surgically remediable epilepsies

So many new antiepileptic drugs have been introduced in the past two decades that it would now literally take a lifetime to prove the inability of each drug, alone and in combination, to stop seizures in any individual patient. Consequently, true medical intractability, or pharmacoresistance, is an impractical concept for selecting surgical candidates. A major advance in the field of epilepsy surgery, therefore, has been the identification of specific epilepsy syndromes that are *surgically remediable* [100] (Table 60.1). Best patient care requires identification of such patients early in the course of their disorders, as soon as first-line antiepileptic medications fail, and referral to epilepsy surgery centres at

Table 60.1 Surgically remediable epilepsy syndromes.

Characteristic features
Known pathophysiology
Predictable natural history
Unresponsive to pharmacotherapy
Progressive features (e.g. developmental delay or interictal behavioural disorders)
Most cost-effective surgical candidates because
Presurgical evaluation can be performed non-invasively
70–90% chance of complete elimination of disabling seizures
Disabling behavioural consequences can be avoided or reversed, but only if surgical intervention is early
Examples
Mesial temporal lobe epilepsy
Epilepsies due to well-circumscribed resectable lesions
Epilepsies in infants and young children due to large or diffuse lesions limited to one hemisphere (e.g. porencephalic cysts, Rasmussen's encephalitis, Sturge–Weber, hemimegencephaly, and other large malformations of cortical development)

Table 60.2 The syndrome of mesial temporal lobe epilepsy.

History
Increased incidence of complicated febrile convulsions or other cerebral insults early in life
Increased incidence of a family history of epilepsy
Onset in second half of first decade of life
Auras common and occur in isolation
Secondary generalized seizures occur infrequently
Seizures often remit for several years until adolescence or early adulthood
Seizures often become medically intractable
Interictal behavioural disturbances can occur (most commonly depression)
Clinical seizure
Aura is usually present. Most common is epigastric rising, often other autonomic or psychic symptoms, with emotion (e.g. fear), can be olfactory, gustatory or non-specific somatosensory sensations (several seconds)
Complex partial seizure. Often begins with arrest and stare, oro-alimentary automatisms and complex automatisms common. Posturing of one upper extremity may occur contralateral to the ictal discharge (1–2 min)
Postictal phase. Usually includes disorientation, recent memory deficit, amnesia for the event and dysphasia if seizures begin in the language-dominant hemisphere (several minutes)
Neurological and laboratory evaluation
Neurological examination usually normal except for memory deficit
Unilateral or bilateral independent anterior temporal EEG spikes, maximum amplitude in basal electrodes
Extracranial ictal EEG activity appears only with complex partial symptoms, usually initial or delayed focal onset pattern of 5–7/s rhythmic activity, maximum amplitude in one basal temporal derivation
Usually temporal lobe hypometabolism on interictal FDG-PET, often involves ipsilateral thalamus and basal ganglia
Usually temporal lobe hypoperfusion on interictal SPECT and characteristic pattern of hyper- and hypoperfusion on ictal SPECT
Usually material-specific memory disturbances on neuropsychological testing and amnesia with contralateral intracarotid sodium amytal injection
Hippocampal atrophy usually visible on MRI

Adapted from ref. 121 with permission.

EEG, electroencephalogram; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Table 60.3 Common surgical procedures for epilepsy and numbers performed worldwide between 1986 and 1990.

Procedure	Number of patients (%)
Anterior temporal resections	4862 (59)
Amygdalohippocampectomy	568 (7)
Extratemporal resection	1073 (13)
Lesionectomy	440 (5)
Hemispherectomy and large multilobar resections	448 (5)
Corpus callosotomy	843 (10)
Total	8234 (100)

From ref. 4 with permission.

a time when surgical intervention provides the greatest opportunity for curing the epilepsy condition and preventing the appearance of irreversible adverse psychological and social consequences. The prototype of a surgically remediable epilepsy syndrome is MTLE, particularly when it is associated with hippocampal sclerosis (Table 60.2). Other examples include limbic and neocortical epilepsies due to well-circumscribed structural lesions that can be easily resected, and certain childhood syndromes amenable to large multilobar resections or hemispherectomy, such as Sturge–Weber syndrome, Rasmussen's encephalitis, hemimegencephaly, large porencephalic cysts and catastrophic secondary generalized epileptic disorders of infancy and early childhood due to localized areas of cortical dysplasia. In such patients, surgery can usually be recommended with minimal, non-invasive, presurgical evaluation, and outcome is excellent by definition; therefore, continuing exhaustive trials of antiepileptic medications unnecessarily delays a definitive therapeutic intervention. Patients with medically refractory symptomatic epilepsies who do not have surgically remediable epilepsy syndromes, as defined here, may still be candidates for surgical intervention. For these patients, the underlying substrate is more complicated, chronic intracranial recordings most likely will be necessary, and there is less of a chance that they would be become seizure free than if they had a surgically remediable syndrome. It may, therefore, be reasonable to continue pharmacotherapy longer in this group of patients, and surgical treatment may not be sufficiently cost-effective to warrant pursuing such therapy in developing countries with limited resources.

Types of surgical treatment for epilepsy

The surgical treatments commonly used for epilepsy are shown in Table 60.3, with the numbers of each procedure performed worldwide between 1986 and 1990, when the last global survey was taken. Most surgical procedures involve resection of a presumed epileptogenic region. The area of resection may be standardized, determined by what is assumed to be a pathophysiological mechanism common to all patients with a particular form of epilepsy, or it may be tailored to the particular needs of each patient. Other surgical interventions

include disconnection, ablation and chronic stimulation. Surgical therapy for epilepsy can require awake procedures, and specialized anaesthetic approaches are often required (see Chapter 80).

Standardized resections

Examples of standardized resections include amygdalohippocampectomy and hemispherectomy (see Chapters 69 and 73). The former approach was designed to remove the least amount of tissue responsible for spontaneous complex partial seizures originating in mesial temporal structures. Evidence suggests that inclusion of the parahippocampal gyrus is important for successful results of amygdalohippocampectomy [101]. Performance of a hemispherectomy, on the other hand, is based on the assumption that the entire hemisphere is involved in the epileptogenic process, and that so little normal function remains that there is no reason to attempt to spare any particular cortical area. Complete removal of one hemisphere, termed an 'anatomical hemispherectomy', causes a relatively high incidence of late complications, including hydrocephalus and intracranial haemorrhage due to decreased absorption of cerebral spinal fluid by remaining arachnoid villi, and movement of the remaining hemisphere within the cranial vault. Several modifications of the hemispherectomy procedure are currently performed in an attempt to reduce the risk of late complications, and many centres today perform various types of hemispherotomy: removal of a minimal amount of brain tissue, followed by disconnection of the remainder of the hemisphere, leaving it *in situ* (see Chapter 73).

Anterior temporal lobectomies can be either standardized or tailored (see Chapter 69). Early standardized resections removed 4–7 cm of the anterior temporal lobe, including mesial temporal structures, sparing the superior temporal gyrus on the dominant hemisphere. A more recent modification, the anteromesial temporal resection, removes the temporal pole, spares most of the lateral cortex and extends the mesial temporal resection posteriorly. Standardized temporal resections are performed in patients with MTLE because the pathological substrates, usually hippocampal sclerosis, are presumed to create an epileptogenic region that is sufficiently similar from patient to patient that the same resection is generally effective. The presurgical evaluation for a standardized resection need only demonstrate that the patient has the type of epilepsy that responds to the surgical procedure, and that the primary epileptogenic region is within the boundaries of the brain tissue to be removed.

Tailored resections

Tailored temporal lobe resections require presurgical evaluation that identifies not only the location of the epileptic brain tissue, but also its extent. This commonly requires intracranial recordings, either intraoperative interictal spike mapping or extraoperative ictal recordings with subdural grid or depth electrodes (see Chapter 62). There remains controversy, however, concerning the relative values of ictal versus interictal epileptiform abnormalities as guides for determining the extent of a tailored temporal lobe resection, and justification for these added diagnostic procedures in patients with MTLE has been questioned. Nevertheless, there are situations when intracranial recording can suggest active epileptic activity in the posterior temporal region, indicating the need for a more extensive resection, on the one hand, or epileptic activity limited to cortical areas (e.g. the temporal pole, adjacent to a structural lesion that would permit a resection that spares mesial temporal structures), on the other.

Neocortical resections are always tailored, but again there is controversy concerning the relative value of interictal versus ictal epileptiform activity recorded directly from the surface of the brain for determining the extent of tissue to be removed. In some patients, merely removal of a discrete structural lesion (lesionectomy), such as a glioma, is sufficient to eliminate spontaneous ictal events, while in other patients removal of cortical margins is also necessary (see Chapters 70 and 71). Although lesionectomy is clearly the procedure of choice when the epileptogenic lesion is within essential primary cortex, more data are needed to determine what types of epileptogenic lesions are most likely to respond to this conservative approach. A unique application of lesionectomy is removal of hypothalamic hamartomas, which can successfully abolish gelastic seizures (see Chapter 75). In patients with malfunctions of cortical development, such as focal cortical dysplasia and other subtle lesions, MRI may not be helpful and direct cortical recording is necessary to define the epileptogenic zone (see Chapters 72 and 77). Neocortical resections are also tailored to avoid damage to adjacent essential primary cortex that could cause additional neurological deficits. In these situations, functional mapping is necessary, which can be performed intraoperatively (see Chapter 76), or extraoperatively with subdural grid electrodes (see Chapter 62). More recently, functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG) can be sufficient for this purpose in some patients (see Chapters 63 and 64).

Disconnection surgery

Disconnection surgery is performed as a treatment for epilepsy to disrupt propagation along pathways that determine the clinical manifestation of ictal events. The most commonly performed disconnection surgery is corpus callosotomy (see Chapter 74); prevention of interhemispheric propagation appears to abolish or reduce the occurrence of drop attacks due to atonic seizures, brief tonic seizures and myoclonic seizures. Most patients experience beneficial results from an anterior two-thirds callosotomy, which is not likely to be associated with adverse disconnection syndromes. When anterior two-thirds section is unsuccessful, and in patients with severe mental retardation in whom disconnection symptoms would not add to the disability, complete section of the corpus callosum can be performed. Because vagus nerve stimulation (VNS) can be effective against drop attacks, this less invasive approach is now usually tried *before* callosotomy, and there has been a decrease in the number of patients undergoing corpus callosotomy in recent years (see Chapter 81).

Multiple subpial transection (MST) disconnects corticocortical fibres in order to prevent lateral spread of epileptic activity while retaining the structure of cortical columns responsible for func-

tion (see Chapter 75). This procedure can be carried out in primary motor and language cortices, with little or no neurological deficit, and can be effective in eliminating or reducing seizure generation. It is most often used in combination with a tailored cortical resection, when the epileptogenic region encroaches on primary essential cortex and cannot be completely removed, but occasionally has been successfully used alone. Recent studies suggest that the effectiveness of MST is not as great as had originally been reported.

Stereotactic ablative surgery and stimulation

Stereotactic ablative surgery is also performed in some patients with epilepsy (see Chapter 78). Although amygdalotomy is no longer considered to be effective, there is increasing interest in the use of the gamma knife not only as a treatment for focal neocortical lesions, but also for MTLE (see Chapter 83). Continuous deep brain stimulation, targeting various subcortical structures, as well as response stimulation, which employs electrodes implanted into the epileptogenic region and connected to a device embedded in the skull that detects ictal onset and delivers an abortive stimulus, are promising experimental approaches currently under investigation (see Chapter 82). Gamma knife ablation and stimulation remain experimental therapies. Other investigative approaches to surgical treatment are discussed in Chapter 84.

Presurgical evaluation

Definition of terms

Clarification of terminology used for identifying abnormalities associated with an epileptogenic area of the brain has aided development of multidisciplinary presurgical evaluation protocols [102] (Table 60.4). When resective surgery is planned, presurgical evaluation is aimed at identifying the *epileptogenic zone*, which is defined as the area of brain necessary and sufficient for generating spontaneous seizures. This, therefore, is the minimal amount of brain tissue that must be removed to eliminate habitual seizures. The epileptogenic zone is a theoretical concept, and its boundaries cannot be accurately identified; however, they can be approximated by a variety of diagnostic procedures that define other areas of abnormality associated with the epileptogenic zone.

The *irritative zone* is that area of cortex that generates interictal spikes. Although the scalp electroencephalogram (EEG) in some patients can reveal a single EEG spike focus, defined as the area where interictal spike amplitude is maximal, direct recording from brain with depth, subdural strip or grid electrodes reveals that these scalp transients reflect widespread cortical generators (see Chapters 61 and 62). The irritative zone, therefore, can be extensive, and multiple irritative zones may exist. For instance, in MTLE it is common for interictal spikes to be recorded independently from both mesial temporal areas. Functional MRI (fMRI) with EEG is now being used to identify anatomical substrates of the irritative zone (see Chapter 66). The irritative zone is usually much larger than the epileptogenic zone.

The *ictal onset zone* refers to that area of cortex where initial EEG ictal discharges are recorded. Whereas a characteristic sphenoidal ictal onset pattern has a high correlation with mesial temporal ictal onsets [103], and scalp electrodes can occasionally identify the site of onset of neocortical seizures, precise definition of the ictal onset zone often requires intracranial electrodes (see Chapters 61 and 62). In some circumstances, propagation at seizure onset is rapid, and areas of early propagation might also be considered part of the epileptogenic zone. Identification of the ictal onset zone helps to localize the epileptogenic zone, but it is uncertain how this information can contribute to determining its actual extent. Ictal SPECT and fMRI can now also be used to help delineate the ictal onset zone (see Chapters 64 and 65).

The *epileptogenic lesion* is the structural abnormality believed to cause the epilepsy condition. This can include hippocampal sclerosis, malformations of cortical development, neoplasms, congenital defects, scars, vascular malformations, cysts and all

Table 60.4 Definition of abnormal brain areas.

	Definition	Measures
Epileptogenic zone	The area of brain that is necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures	Theoretical concept
Irritative zone	Area of cortex that generates interictal spikes	Electrophysiological (invasive and non-invasive)
Ictal onset zone	Area of cortex where seizures are generated (including areas of early propagation under certain circumstances)	Electrophysiological (invasive and non-invasive)
Epileptogenic lesion	Structural abnormality of the brain that is the direct cause of the epileptic seizures	Structural imaging and tissue pathology
Symptomatogenic zone	Portion of the brain that produces the initial clinical symptomatology	Behavioural observation and patient report
Functional deficit zone	Cortical area of non-epileptic dysfunction	Neurological examination, neuropsychological testings, EEG, PET, SPECT

From ref. 102 with permission.

EEG, electroencephalogram; PET, positron emission tomography; SPECT, single photon emission computed tomography.

other pathological substrates for epilepsy. For some lesions, such as hippocampal sclerosis, the ictal onset zone can be within the lesion; for others, seizures begin adjacent to the lesion; while in still others, EEG epileptiform abnormalities can be most prominent at a distance from the lesion. Although the epileptogenic zone includes the epileptogenic lesion, the former is usually more extensive than the latter. Surgical results are poor if the epileptogenic lesion is not entirely removed; however, there are exceptions, as with schizencephaly, where only part of this extensive lesion is usually epileptogenic and localized subtotal removal can eliminate seizures [104]. Most epileptogenic lesions can now be identified by high-resolution MRI, but some are diagnosed only on pathological evaluation of resected tissue (see Chapter 64). It is important to note that patients with focal seizures can occasionally have incidental structural lesions that are not epileptogenic and therefore do not help in defining the epileptogenic zone.

The *symptomatogenic zone* refers to the area of brain responsible for generating the initial clinical symptoms. Frequently, the epileptogenic zone is in a so-called 'silent area' of the brain, and ictal symptoms reflect propagated discharges. In these situations, the symptomatogenic zone is not within the epileptogenic zone; however, identification of the symptomatogenic zone can help determine propagation pathways that confirm the location of the epileptogenic zone defined by other data.

Areas of epileptogenicity in the brain are also associated with non-epileptic dysfunction that can appear as neurological or cognitive deficits on neurological or neuropsychometric examinations (see Chapter 67), non-epileptic EEG abnormalities (see Chapters 61 and 62), areas of hypometabolism on FDG-PET and areas of hypoperfusion on SPECT (see Chapter 65). These non-epileptic disturbances define a zone that reflects disturbances directly due to the epileptogenic lesion, as well as areas that undergo enduring changes due to ictal generation and propagation. Consequently, the *functional deficit zone* can be much larger than the epileptogenic zone, although in some patients there is no identifiable functional deficit zone.

The battery of diagnostic tests that constitute the presurgical evaluation is determined in part by the type of epilepsy or epileptic seizures exhibited by the surgical candidate, and in part by the type of surgical procedure to be performed. For instance, estimates of the location and extent of the epileptogenic zone are necessary when surgical resection is planned; however, this need not be exact for large standardized resections, such as hemispherectomies, should be limited to mesial and anterior temporal lobe for standardized anteromesial temporal resections, and must be localized specifically to mesial temporal structures for amygdalocampectomies. On the one hand, precise delineation of the extent of the epileptogenic zone is necessary when tailored resections are to be undertaken, but, on the other, this is not necessary at all for lesionectomy, or when corpus callosotomy is intended, except as required to rule out the possible benefit of a more definitive resective procedure. In infants and small children, larger tailored resections can be performed without producing irreversible neurological deficit, because of the plasticity of the developing brain. Furthermore, localization of the epileptogenic zone is difficult; therefore, the risk and expense of chronic intracranial electrophysiological recordings to more precisely identify the boundaries of an epileptogenic zone may not be as justified as in older patients undergoing tailored resections (see Chapter 77).

Candidate selection

Identification of potential surgical candidates requires a detailed history, including a description of all habitual epileptic seizures, a neurological examination, and psychiatric and social evaluations. This leads to (1) a presumptive diagnosis of epileptic seizures and, if possible, an epilepsy syndrome; (2) an impression of the likelihood that surgical intervention will be of benefit; and (3) insight into the most appropriate surgical procedure to be considered. Psychosocial issues are important for determining how the patient will respond to presurgical evaluation and surgical treatment, and whether improvement or cure of the epileptic condition will have sufficient impact on quality of life to justify the risks and expense. Psychopathology, such as depression, may even predict seizure outcome (see Chapter 68). Patients are not considered candidates for surgical treatment if they have an underlying neurodegenerative disease or there is a medical contraindication to surgery. An intelligence quotient (IQ) below 70 suggests widespread brain involvement and is likely to be associated with a diffuse or bilateral epileptogenic zone, so this is a relative contraindication for localized resective surgery. Mental retardation is not a contraindication for corpus callosotomy, and developmental delay is actually an indication for hemispherectomy or multilobar resection in infants and small children, in whom psychomotor deterioration can be reversed by a beneficial surgical procedure (see Chapter 77). Chronic psychosis is also a relative contraindication for surgical treatment, because the psychotic symptoms do not usually resolve, even when surgery is effective in abolishing epileptic seizures. However, there is no evidence that the surgical treatment makes psychosis worse (see Chapter 68). Therefore, successful surgical intervention simplifies management and improves quality of life to the extent that it can be justified in some psychotic patients, even though they will remain disabled. It is important in this situation to distinguish between patients with chronic psychosis and those with seizure-related psychotic symptoms, such as postictal psychosis, because in this situation surgical intervention that eliminates seizures will also eliminate the psychotic behaviour.

Non-invasive tests of epileptic abnormalities

The electrophysiological presurgical evaluation begins with the interictal EEG (see Chapter 61). Localized interictal spike discharges help to define the irritative zone, and localized non-epileptiform abnormalities, such as slowing and attenuation of normal rhythmic activity, help to identify the functional deficit zone. Neuroimaging is now an essential part of the initial presurgical evaluation. High-resolution MRI identification of hippocampal atrophy and/or hyperintensity on T2 imaging, as well as hypometabolism on FDG-PET, correlate highly with the presence of hippocampal sclerosis (see Chapters 64 and 65). In patients with neocortical focal epilepsy, high-resolution MRI will now usually identify a structural lesion, but when MRI is negative, FDG-PET can still reveal focal hypometabolism of the

epileptogenic zone, particularly in cases of focal cortical dysplasia (see Chapter 65).

Patients with neuroimaging evidence of a focal abnormality spatially consistent with the seizure semiology are likely to have a surgically remediable epilepsy syndrome, particularly when interictal EEG spikes are predominantly localized to the same area. The next step in the presurgical evaluation is inpatient video-EEG monitoring to capture spontaneous seizures (see Chapter 61). If MTLE is suspected, basilar electrodes are used. Although sphenoidal electrode placements were recommended in the past, T1T2 surface placements appear to be equally useful for most patients, and sphenoidals are now used mainly when results with these electrodes are equivocal. A typical 5–7 Hz build-up of activity in one basal electrode, within 30 s of a more diffuse (but not contralateral) EEG change, is highly diagnostic of ictal onset in the ipsilateral hippocampus; however, such patterns can be falsely lateralizing, particularly when the involved hippocampus is severely atrophic (the burned-out hippocampus). Ictal EEG onset patterns are less useful for neocortical epileptogenic regions, but usually provide lateralizing information at least. Although it has been argued that inpatient video-EEG monitoring is not always necessary, particularly when there is excellent correlation among seizure semiology, a focal structural lesion on MRI and focal interictal EEG spikes, in most patients ictal recordings are also important to ensure that the events in question are not psychogenic non-epileptic seizures.

Neurocognitive testing provides additional information concerning the location and extent of the functional deficit zone (see Chapter 67). A routine battery of psychometric tests is used, particularly to distinguish between temporal lobe and frontal lobe disturbances and to lateralize these disturbances to the language-dominant or non-dominant hemisphere.

Information regarding the location of the irritative zone can now be reliably obtained with magnetoencephalography (MEG) (see Chapter 63), as well as EEG fMRI (see Chapter 64). Information concerning the location of the ictal onset zone can be obtained with ictal SPECT (see Chapter 65), and occasionally with MEG or fMRI when patients have seizures in the magnet. Localized functional and structural abnormalities can also be identified with MR spectroscopy (MRS), and functional deficit zones may be obtained by mapping cortical functions with fMRI (see Chapter 64). At present, all of these tests are considered to be confirmatory, and are usually used in patients who are not considered surgical candidates on the basis of non-invasive evaluation alone, in order to help determine the placement of intracranial electrodes for invasive evaluation.

Intra-arterial amobarbital procedures (IAP) are used to (1) determine hemispheric dominance for language; (2) confirm that the temporal lobe contralateral to an anterior temporal lobe resection can support memory; and (3) evaluate memory function in the temporal lobe ipsilateral to a presumed mesial temporal epileptogenic region (see Chapter 67). When IAP reveals that language dominance is in the right hemisphere, particularly in a right-handed patient, this suggests a left hemisphere functional deficit, confirming other evidence for an epileptogenic zone in the left hemisphere. When one temporal lobe is unable to support memory, this suggests a functional deficit zone that confirms a suspected epileptogenic region in that temporal lobe. Most centres still consider the IAP necessary to demonstrate that the hemisphere contralateral to a planned mesial temporal resection can support memory. It is becoming increasingly difficult to perform the IAP in many countries, however, because of a chronic shortage or unavailability of amobarbital. fMRI is now considered adequate for demonstrating hemispheric dominance for language, but has not yet provided a reliable way to confirm unilateral hippocampal dysfunction. Etomidate has been successfully used in some centres as a substitute for amobarbital (see Chapter 67).

Invasive testing

If the tests discussed above are not concordant, or fail to yield sufficient information to identify the location of the epileptogenic zone, but a reasonable hypothesis can be made concerning the likely location of a resectable epileptogenic zone, intracranial recordings can usually provide the additional necessary localizing information (see Chapters 62 and 78). Stereotactically implanted depth electrodes are the usual chronic recording technique preferred when the hypothesis for the epileptogenic zone includes the mesial temporal area, or deep neocortical areas that are not easily approached from the surface of the brain. Otherwise, subdural grid or strip electrodes can be used. The former provide a much more extensive cortical coverage and are necessary when there is a need for functional mapping, but these electrodes require a craniotomy and are usually only placed when the epileptogenic zone has been reliably lateralized. Subdural strip electrodes can be inserted through burr holes, so they can be placed bilaterally, and can also be placed under the temporal lobe to approximate mesial temporal areas as an alternative to depth electrodes. In some institutions, a semi-invasive approach utilizes foramen ovale electrodes, which can be inserted percutaneously into the ambient cistern to record from mesial temporal structures; however, they provide no invasive information regarding seizures that might originate outside this area [105]. Because interpretation of ictal EEG onsets with subdural grid electrodes is difficult, when additional information is required to determine the extent of the epileptogenic zone for a tailored neocortical resection, most centres now prefer intraoperative mapping of interictal EEG spikes to chronic invasive recording. Functional mapping can also be adequately performed intraoperatively, except in small children and the rare patient with limited capacity to cooperate under these conditions (see Chapter 76).

Diagnostic tests under investigation

There are a number of experimental techniques that may be useful in the future for defining the epileptogenic zone (see Chapter 66). A variety of neurophysiological procedures and novel PET tracers have demonstrated utility in identifying either the epileptogenic zone or an associated functional deficit zone. Optical imaging makes use of light reflectants to measure the state of neuronal activation, and can be used intraoperatively to visualize epileptic cortical activity [106]. Animal studies suggest the possibility that this technique might eventually be applicable through the intact skull. One experimental invasive technique involves implantation of microdialysis probes, which permit sampling of extracellular fluid before, during and after seizures [107].

There has been considerable recent interest in biomarkers of epileptogenesis and epileptogenicity. Biomarkers that indicate epileptogenesis would be useful for identifying not only patients at risk for epilepsy, but also patients with epilepsy who may have progression of their condition and, therefore, may be candidates for early surgical treatment. Interictal biomarkers that reliably delineate epileptogenic tissue could make it possible to determine the location and extent of the epileptogenic region without the need for expensive inpatient telemetry to capture seizures. Two such biomarkers are currently under investigation. One is the PET ligand α-methyl-tryptophan (AMT), which can, in some patients with seizures due to tuberous sclerosis who have multiple tubers, identify the one responsible for generating seizures [108]. AMT-PET has also been used to identify the epileptogenic region in other forms of focal epilepsy [109]. The other is high-frequency oscillations (HFOs) associated with interictal spikes and ictal onsets, particularly those in the frequency range of 200–600 Hz, termed fast ripples (FR) (see Chapter 62). FR recorded with microelectrodes from hippocampus and parahippocampal structures of patients with MTLE, and animal models of this condition, appear to be unique to areas that generate spontaneous seizures [110]. Recent investigations indicate that FR can also be recorded with standard depth and subdural electrodes, and that they have the same significance for neocortex as they do for hippocampus [111,112]. For HFOs to be most useful for presurgical evaluation, it would be necessary to devise ways to identify them non-invasively. It may be possible to do this with MEG, or there may be correlates of interictal spikes associated with FR on EEG-fMRI that are different from EEG-fMRI correlates of interictal spikes that are not associated with FR (see Chapter 66). Another promising technique involves statistical parametric mapping (SPM) of hippocampus and neocortex thickness mapping, which permits identification of discrete patterns of atrophy not apparent on visual analysis of MRI or volumetry [113,114]. FR appear to be uniquely associated with discrete areas of hippocampal atrophy [115], suggesting that these structural abnormalities could reliably identify epileptogenic areas.

Strategy for presurgical evaluation

Localized resections

When patients with suspected MTLE are considered for standardized anteromesial temporal resection, the presurgical evaluation begins with interictal EEG to identify the irritative zone, and MRI to localize an epileptogenic lesion (see Chapter 69). In many centres today, an FDG-PET scan is also performed to localize a functional deficit zone in the appropriate temporal lobe, while some centres prefer ictal SPECT. Inpatient video-EEG monitoring is then carried out to characterize the ictal EEG onset. If a localized mesial temporal ictal onset correlates with a mesial temporal lesion on MRI, or temporal hypometabolism on FDG-PET, and there are no confounding features from interictal EEG, seizure semiology, neuroimaging or neurocognitive studies, patients usually undergo IAP, and if the contralateral hemisphere supports memory, a standardized anteromesial resection can be performed. In some centres, if there is clear evidence of hippocampal sclerosis on MRI, and temporal hypometabolism on FDG-PET as well, only a lateralized EEG onset is required for anteromesial temporal resections without invasive testing. Most centres require more invasive information if amygdalohippocampectomy is intended, to ensure that the epileptogenic zone is not in temporal neocortex.

Tailored resections, either temporal lobe or extratemporal, require an initial non-invasive approach similar to that discussed above (see Chapters 69–72). However, additional evaluation is required to determine the extent of the epileptogenic zone. Furthermore, if the suspected epileptogenic zone is adjacent to essential cortex, functional mapping is also necessary. Specific delineation of the epileptic abnormality and functional mapping are achieved either by chronic subdural grid or by intraoperative recording and stimulation. If the results of invasive studies reveal that the epileptogenic zone includes primary essential cortex that cannot be resected, lesionectomy is one option, and MST of the epileptically involved essential cortex is another (see Chapter 75).

Multilobar resections and hemispherectomy

Patients with severe hemispheric dysfunction and unilateral seizures who are candidates for hemispherectomy or hemispherotomy require interictal and ictal EEG studies to confirm that the dysfunctional hemisphere is a source of epileptic activity, and that no seizures originate contralaterally (see Chapters 73 and 77). Structural imaging usually, but not always, demonstrates atrophy or other extensive pathology in the dysfunctional hemisphere. FDG-PET not only confirms the dysfunction by demonstrating hypometabolism of the involved hemisphere, but is also of value in determining that the metabolic activity of the contralateral hemisphere is normal. Evoked potentials can be used to identify residual function in the epileptogenic hemisphere. In some instances, when the occipital lobe appears structurally and functionally normal, and does not generate interictal spikes, a subtotal hemispherectomy may be performed, sparing the posterior visual cortex and pathways.

Multilobar resections are not only performed as subtotal hemispherectomies, but also as a form of tailored resections when the presurgical evaluation indicates that the epileptogenic zone is likely to involve parts of more than one lobe. In some centres, anterior temporal lobe resections are combined with partial frontal lobe resections when the ictal onset reveals rapid projection of the initial ictal discharge from one to the other.

Multilobar resections are also performed in infants and young children with secondary generalized catastrophic epilepsy when MRI and FDG-PET reveal large unilateral lesions, usually malformations of cortical development in the posterior brain area. In these patients, the interictal and ictal EEG and seizure semiology are often of little value in localizing the epileptogenic region; however, non-epileptic EEG abnormalities, such as asymmetrical sleep spindles, increased slowing or even attenuation of generalized epileptiform transients, are more likely to identify the epileptogenic zone. Intraoperative electrocorticography is usually necessary for delineation of the area to be resected.

Corpus callosotomy

Localization of the epileptogenic region is obviously not necessary for performing corpus callosotomy (see Chapter 74). Neverthe-

less, patients with drop attacks as the most disabling feature of a secondary generalized epileptic disorder are evaluated with interictal and ictal EEG, as well as structural and often functional imaging and neuropsychological testing, in order to be certain that there is no localized epileptogenic zone that would be amenable to a more definitive resection.

Ablative surgery and stimulation

Localization of the epileptogenic region, as discussed previously, is necessary prior to gamma knife ablation, and also for response stimulation, because electrodes need to be placed in the epileptogenic zone (see Chapters 82 and 83). It is possible to carry out response stimulation with electrodes in more than one epileptogenic zone, even when these areas are bilateral. Because deep brain stimulation is not dependent on the location of the epileptogenic zone, presurgical evaluation, as for corpus callosotomies, is merely necessary to confirm that the patient is not a candidate for a more definitive localized surgical resection.

Outcome

Outcome assessment is essential for evaluating the sensitivity and specificity of presurgical diagnostic tests and the efficacy of surgical interventions. Improvements in surgical treatment for epilepsy ultimately need to be validated by quantitative data on outcome, which also aid in improving the selection of appropriate candidates for the various surgical procedures. Outcome is measured with respect to not only the epileptic seizures, but also health-related quality of life (HRQOL), cognitive and social function and surgical complications.

Outcome with respect to seizures

Most centres currently utilize the seizure outcome classification shown in Table 60.5 from the Palm Desert conferences [38]. Although the alternative International League Against Epilepsy classification, shown in Table 60.6, is also used, it requires accurate documentation of preoperative seizure frequency [116].

Table 60.7 indicates outcome with respect to seizures for mesial temporal resections, neocortical resections, hemispherctomies and corpus callosotomies, obtained from a worldwide survey carried out in 1986, and another in 1991, when the last such survey was performed [38]. These data show a definite increase in the percentage of patients becoming seizure free, and a decrease in those not improved following anterior temporal lobectomy, in the more recent survey, suggesting that improvements in diagnostic

Table 60.5 Classification of postoperative outcome.

Class I: free of disabling seizures[a]
Completely seizure free since surgery
Non-disabling simple partial seizures only since surgery
Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
Generalized convulsions with antiepileptic drug discontinuation only
Class II: rare disabling seizures ('almost seizure free')
Initially free of disabling seizures but has rare seizures now
Rare disabling seizures since surgery
More than rare disabling seizures since surgery, but rare seizures for the last 2 years
Nocturnal seizures only
Class III: worthwhile improvement[b]
Worthwhile seizure reduction
Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not <2 years
Class IV: no worthwhile improvement
Significant seizure reduction
No appreciable change
Seizures worse

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[a] Excludes early postoperative seizures (first few weeks).

[b] Determination of 'worthwhile improvement' will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function and quality of life.

Table 60.6 ILAE proposal for a new classification of outcome with respect to epileptic seizures.

Classification	Definition
1	Completely seizure free; no auras
2	Only auras; no other seizures
3	One to three seizure days per year; ± auras
4	Four seizure days per year to 50% reduction of baseline seizure days; ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

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Table 60.7 Outcomes before 1985 and from 1986 to 1990.

		Number of patients (%)			
		Seizure free	Improved	Not improved	Total
Limbic resections					
Before 1985		1296 (55.5)	648 (27.7)	392 (16.8)	2336 (100)
1986–1990	ATL	2429 (67.9)	860 (24.0)	290 (8.1)	3579 (100)
	AH	284 (68.8)	92 (22.3)	37 (9.0)	413 (100)
Neocortical resections					
Before 1985		356 (43.2)	229 (27.8)	240 (29.1)	825 (100)
1986–1990	ETR	363 (45.1)	283 (35.2)	159 (19.8)	805 (100)
	L	195 (66.6)	63 (21.5)	35 (11.9)	293 (100)
Hemispherectomies					
Before 1985		68 (77.3)	16 (18.2)	4 (4.5)	88 (100)
1986–1990	H	128 (67.4)	40 (21.1)	22 (11.6)	190 (100)
	MR	75 (45.2)	59 (35.5)	32 (19.3)	166 (100)
Corpus callosotomies					
Before 1985		10 (5.0)	140 (71.0)	47 (23.9)	197 (100)
1986–1990		43 (7.6)	343 (60.9)	177 (31.4)	563 (100)

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AH, amygdalohippocampectomy; ATL, anterior temporal lobectomy; ETR, extratemporal resection; H, hemispherectomy; L, lesionectomy; MR, large multilobar resection.

approaches, including long-term EEG monitoring with basal electrodes and structural and functional imaging, have had a positive impact on the results of this procedure. These data also reveal that amygdalohippocampectomy and neocortical resections that include an epileptogenic lesion, only tabulated in the later series, are associated with an outcome with respect to epileptic seizures that is similar to that for anterior temporal lobectomy.

The results of extratemporal resection reveal no change in the percentage of patients becoming seizure free between the two surveys; however, there is a reduction in the percentage of patients not improved in the later series. With the widespread use of subdural strip and grid recordings for extratemporal resections after 1985, however, there have been many patients who received this surgical procedure based on electrophysiological evidence alone who would not have been considered surgical candidates prior to 1985. These patients, who do not have obvious structural lesions, do not do as well as patients with structural lesions, and account for the fact that there was no significant improvement in the percentage of patients who became seizure free. On the other hand, these new techniques appear to have reduced the number of patients who have inappropriate surgical resection and end up with no benefit.

In contrast to the outcome data for patients undergoing localized resections, patients with hemispherectomies and corpus callosotomies had poorer results in the more recent series compared with results obtained prior to 1985. It is important to note, however, that there has been a considerable increase in the number of patients who undergo these procedures, largely due to the fact that modified hemispherectomies greatly reduced the incidence of late complications, and that microsurgical approaches to corpus callosotomy, as well as the increased use of only anterior two-thirds section, greatly reduced occurrence of the disconnection syndrome. Consequently, both hemispherectomy and corpus callosotomy were being applied to a much larger group of patients for whom the risk prior to 1985 would have been too great to be justified by the chance of benefit. Because many more patients underwent these surgical interventions between 1985 and 1990 than previously, and most experienced some benefit while very few suffered severe complications, the advances in diagnostic and surgical technology also resulted in overall improved results. Continued improvements in outcome for these procedures are documented in Chapters 73 and 74.

More recently, the Western Ontario RCT [35] and the AAN practice parameter [37], which was a meta-analysis of 24 non-overlapping surgical series published between 1990 and 2000, also showed two-thirds of patients seizure free after temporal resections for TLE. The meta-analysis also evaluated neocortical resections and found 50% of patients seizure free, similar to results in Table 60.7. Although the AAN permitted the recommendation that temporal resection is the treatment of choice for pharmacoresistant TLE, they did not permit a similar recommendation for neocortical resections, because there was no RCT; however, given the similarities of outcome results among the RCT, the meta-analysis, and the figures in Table 60.7 for TLE, there is no reason to believe that the meta-analysis and Table 60.7 outcome figures for neocortical surgeries are any less biased. More recent published series of surgery for TLE have provided even better results.

Outcome with respect to seizures is more complicated than most studies would suggest, because a certain percentage of patients tend to relapse or remit over time. Relatively few long-term studies have been carried out, and these will be necessary in the future in order to fully understand the beneficial effects of surgical intervention [99,117].

Quality of life, cognitive and social outcomes

There are numerous ways of assessing quality of life in epileptic patients, but most studies today utilize one of the three versions of the Quality of Life in Epilepsy (QOLIE) scale, which was specifically designed to measure HRQoL in surgical series [118]. The Western Ontario RCT found quality of life to be significantly better in surgical patients than in those treated medically by the end of 1 year of follow-up, and there was a trend towards improved social function at that time measured by percentage of patients in school and employed [36]. The meta-analysis carried out for the AAN practice parameter included studies that utilized a variety of different instruments to assess HRQoL, and found this measure to be most improved if temporal or extratemporal resection eliminated all seizures [37]. However, in one study, HRQoL was not as good in patients who continued to have auras as in patients who were completely seizure free, but better than in patients who continued to have disabling seizures [119]. Transient psychiatric disturbances, most commonly depression, occurred in 25–40% of patients during the postoperative year, whether or not they were seizure free, but *de novo* psychiatric symptoms, which were rare, were much more common in patients whose seizures continued (see Chapter 68). Verbal memory deficits were the most common postoperative cognitive disturbances following mesial temporal resections in the language-dominant hemisphere, particularly in patients whose verbal memory was normal preoperatively. Conversely, verbal memory improved after successful non-dominant temporal lobe surgery, and many patients who became seizure free postoperatively experienced an increase in IQ (see Chapter 67). Patients with pharmacoresistant epilepsy are often unemployed or underemployed; however, published studies were inconsistent with respect to whether successful surgical treatment improves their employment situation. In older studies, this is probably due to the fact that patients had seizures for many years prior to surgery, and were sufficiently disabled during critical periods of social and vocational development that they did not possess the skills to become employed and live independently, even if surgery relieved them of their seizures. It is anticipated that, with earlier interventions before psychological and social disabilities become irreversible, successful surgery will permit many patients to live relatively normal, independent lives. The practice parameter found that after temporal lobe resections, 79% of patients operated a motor vehicle, compared with 20% preoperatively, and 88% were living independently, compared with 68% preoperatively [37]. There is also evidence that mortality rate is reduced in patients who are seizure free post operatively [120], and the one patient who died during the Western Ontario RCT was in the medical arm of the study [35].

Surgical complications

The AAN practice parameter meta-analysis identified seven publications that permitted adequate analysis of surgical complica-

tions in 556 patients [37]. Two deaths occurred within 1 month of surgery, one due to trauma and the other not described. Six per cent of patients experienced new neurological deficits consisting of mild aphasias, cranial nerve III and IV palsies, visual field deficits greater than a quadrant and hemiparesis. Half of these resolved within 3 months and the other half were considered permanent. Most of the aphasias were receptive following temporal resections, and the hemipareses developed following cortical resections adjacent to motor cortex. Postoperative infections occurred in 5% of patients, most commonly in the wound, but also including meningitis and at least one brain abscess. Only one deep vein thrombosis was reported, and hydrocephalus occurred in three patients with large resections. Surgical complications are discussed in more detail in Chapter 79.

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61 Scalp EEG in the Epilepsy Surgery Evaluation

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Introduction

Electroencephalography has been a central diagnostic test in epilepsy since the 1930s, and its role in the presurgical evaluation of patients with medically intractable epilepsy continues to be paramount. The goal of the presurgical evaluation is to identify the putative epileptogenic zone, which is the area of cortex that is necessary and sufficient for the generation of clinical seizures. This zone is operationally defined as the minimum amount of tissue that, if removed, would result in seizure cessation. Therefore, confirmation of the location, but not necessarily the extent, of the epileptogenic zone is best accomplished when the patient has achieved seizure freedom after a surgical resection. Nonetheless, preoperative identification of the putative epileptogenic zone is necessary, and this includes evaluation of the ictal behaviour and the interictal and ictal scalp electroencephalogram (EEG). Such analysis is conducted in concert with a variety of other diagnostic modalities assessing structure and function including high-resolution MRI, interictal fluorodeoxyglucose (FDG)-positron emission tomography (PET), ictal single photon emission computerized tomography (SPECT), neurocognitive testing, and sometimes magnetoencephalography (MEG) and functional MRI (fMRI) (see Chapters 62–66). The role of the EEG has changed over time with the additional structural and functional information that is provided by more recently developed investigative studies, and this has allowed for more patients to be eligible for epilepsy surgery and to proceed to resective surgery without the need for intracranial electroencephalographic monitoring (see Chapter 62). In patients for whom intracranial monitoring is necessary, scalp electroencephalography plays an integral role in planning the electrode placement locations.

Technical considerations

Scalp electrodes

Because focal epilepsy commonly arises from the mesial temporal region, additional electrodes are often added to the standard electrode locations specified by the international 10–20 electrode placement system. These electrodes consist of cheek (T1/T2), mastoid or sphenoidal electrodes, or, less commonly, foramen ovale electrodes. Although the use of these supplementary electrodes may facilitate the identification of mesial temporal epileptiform discharges, there is debate as to whether indwelling sphenoidal electrodes are more sensitive than surface basilar electrodes. In a study by Binnie *et al.* [1], 111 patients with epilepsy were evaluated with both sphenoidal and cheek electrodes. In 17 patients a superficial cheek electrode recorded all discharges seen at the sphenoidal electrode. For all but 2 out of 165 epileptic foci, cheek electrodes detected more than 90% of the discharges detected by the sphenoidal electrodes, which suggests that sphenoidal recordings conferred no meaningful advantage in the detection of interictal epileptiform discharges over anterior temporal cheek electrodes. In contrast, others have reported sphenoidal recordings to be superior to temporal scalp electrodes in ictal recordings. Pacia *et al.* [2] found that in 3 out of 31 patients all seizures appeared in the sphenoidal electrode at least several seconds (range 4–31 s) before the appearance in the temporal scalp electrodes. The opposite result was observed by Mintzer *et al.* [3], who found that sphenoidal electrodes were not superior to cheek electrodes for detection of seizures with mesial temporal lobe onset in an analysis of 101 ictal tracings in 31 patients with possible temporal lobe epilepsy (TLE). The yield of sphenoidal electrodes may depend, however, on their mode of insertion and the position in relation to the foramen ovale. Kanner *et al.* [4] found that sphenoidal electrodes inserted via fluoroscopic guidance (positioned immediately below the foramen ovale) displayed temporal lobe seizures earlier (≥5 s) and more reliably than did cheek electrodes. Seizure detection increased from 12% of foci among patients with unitemporal foci to 25% among patients with bilateral independent temporal foci, suggesting that carefully inserted sphenoidal leads may clarify ambiguities in some presurgical patients. Although the sensitivity of sphenoidal electrodes may depend on the mode of placement, their utility may decrease over time, depending on the degree of displacement. Wilkus and Thompson [5] found that there was an 8.1- to 8.5-mm displacement over an average of 5 days in place, with the degree of displacement correlating with duration since insertion, not seizure number. The use of indwelling sphenoidal electrodes has decreased over recent years, given the absence of definitive benefit from them, the discomfort of their insertion and their degradation of signal with movement. Similarly, the use of nasopharyngeal electrodes has fallen out of favour.

Additional scalp electrodes interspaced between the 10–20 electrode system also have been used to potentially improve the localization accuracy of scalp EEG [6]. However, approximately 10 cm^2 of cortical surface must be synchronously activated in order for there to be a potential recorded at the surface, and cortical potentials are volume conducted through the skull and

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scalp [7]. This results in significant attenuation and blurring of activity. As such, the use of electrodes in a denser array is not standard or commonly performed.

Types of scalp EEG recording

Most epilepsy surgery centres use dedicated video-EEG monitoring equipment with simultaneous recording of EEG and video to identify the correlation between electrophysiological change and clinical behaviour during seizures. This establishes the diagnosis of epilepsy and helps localize the ictal onset and symptomatogenic zone (cerebral region of the seizure's first behavioural manifestation). The use of digital recording of both EEG and video has become common in recent years, as the cost of data storage has decreased and the quality of digital video recordings has improved. Such systems also allow for data reduction, online processing of the EEG for automatic detection of seizures and interictal epileptiform discharges (IEDs), and offline seizure analysis allowing for more detailed analysis of the spatial and temporal extent of ictal rhythms. Digital EEG also allows for montage reformatting, quantitative analysis of the EEG and digital filtering.

Recording other physiological parameters along with the EEG [including electrocardiogram (EKG), electromyogram (EMG), electro-oculogram (EOG) and respiratory rate] is also useful. Although these other parameters undoubtedly benefit the evaluation of physiological non-epileptic disorders associated with paroxysmal behavioural events, they are also important parameters to evaluate during epileptic seizures because of the physiological changes that accompany seizures. Reported EKG changes include tachycardia, bradycardia, conduction block, repolarization abnormalities and asystole [8]. Such EKG changes can occur around the time or even before the earliest EEG or clinical change and thus can potentially clarify the timing of the seizure onset. Moreover, although the exact relationship between these changes and sudden unexpected death in epilepsy (SUDEP) is not known, screening for serious EKG changes during seizures may benefit the patient's overall clinical care. EKG irregularities may appear in the EEG and can resemble the electrographic pattern of seizures, so including electrocardiography also benefits this possibility within the differential diagnosis.

Occasionally, ambulatory EEG has been used in the presurgical evaluation. Outpatient monitoring may be less informative than inpatient monitoring in some cases due to the inability to safely reduce medications, the inability to repair faulty electrode contacts, the limited video surveillance and the shorter duration of testing. However, ambulatory presurgical electroencephalography monitoring may be useful in a subset of patients. Chang *et al*. [9] reported a group of seven patients who had successful temporal lobe resections after presurgical EEG monitoring that was performed solely on an outpatient basis. Finally, it may be possible in a select number of patients with very frequent seizures, to utilize repeated periods of outpatient recordings (preferably with concomitant video) in order to avoid more costly inpatient testing [10].

Interictal EEG

The localization of IEDs is one means by which to identify the irritative zone, which may be related to the brain area that generates seizures, but also may reflect propagated abnormality or a region that is epileptically abnormal but not capable of generating seizures. As such, the irritative zone may extend beyond the epileptogenic zone. Localization of the irritative zone depends on the neurodiagnostic method used, which includes scalp and intracranial electroencephalography and magnetoencephalography/magnetic source imaging (MSI) [11,12] (see Chapters 62 and 63). IEDs may be infrequent and sometimes do not appear in routine electroencephalography studies of patients with known epilepsy. The yield of observing IEDs is increased with repeated routine EEGs; 50% of patients with interictal epileptiform abnormalities manifest this abnormality in the first EEG, whereas 92% of patients demonstrate it by the fourth EEG [13]. Nonetheless, a small proportion of patients with epilepsy will lack IEDs despite repeated EEGs [14], which may be due to an irritative zone that is not detectable with scalp EEG or the specific epilepsy condition. Long-term monitoring with scalp EEG may help identify rare IEDs in patients with repeatedly normal routine EEGs.

Evaluation of the interictal EEG and identification of the irritative zone is an integral part of the presurgical evaluation. Anterior temporal lobe resection (ATLR) remains the most commonly performed epilepsy surgery (see Chapter 68). Strictly unilateral anterior temporal IEDs have been reported to be associated with higher seizure control rates after ATLR. Walczak *et al*. [14] reported the results of 100 anterior temporal resections for complex partial seizures performed over 21 years and found that the presence of >5% of IEDs outside the surgical area correlated with a poorer outcome in the second postoperative year.

Unilateral focal temporal interictal epileptiform discharges

Several studies have questioned the need for long-term monitoring, particularly in cases of concordant hippocampal sclerosis and unilateral anterior temporal IEDs. For example, Cendes *et al*. [15] studied 184 consecutive patients with TLE and reported that unilateral hippocampal atrophy predicted ipsilateral interictal epileptiform abnormalities and ipsilateral seizure onsets with no false lateralization. The conclusion was that ictal EEG did not provide any additional useful information beyond that of MRI for these patients. As such, bypassing the ictal EEG and its associated hospitalization may be possible if all other data are concordant, and there is a reliable description of ictal behaviour that does not suggest the possibility of non-epileptic seizures (NESs). Others have shown that the concordance of MRI and interictal EEG is closely associated with surgical outcome in mesial TLE [16]. Cambier *et al*. [17] reported a series of 84 patients who underwent ATLR, in which those with unilateral hippocampal atrophy and concordant IEDs were found to be excellent surgical candidates even when long-term monitoring showed discordant or non-localizing ictal recordings. Specifically, 63 out of 69 patients (91%) with confirmatory and 14 out of 15 (93%) patients with non-confirmatory ictal EEG recordings were either seizure free or had only auras at mean follow-up of 24.1 months.

These studies raise the question of whether or not ictal recordings are a prerequisite for surgery in cases of isolated hippocampal sclerosis and unilateral concordant temporal IEDs. However, anterior temporal IEDs can sometimes represent false localization or lateralization from other epileptogenic regions, including

lateral temporal and frontal, parietal and occipital regions, and so localization outside of the mesial temporal lobe also needs consideration [18–21]. As such, ictal recordings remain a standard component of the epilepsy surgery evaluation regardless of the presence of unilateral anterior temporal IEDs and imaging abnormality.

Bilateral independent interictal epileptiform discharges

More than 25% of possible resective epilepsy surgery candidates have bilateral independent temporal IEDs on routine scalp EEG [22]. The degree of lateralization of IEDs in this population may be associated with postsurgical outcome. That is, a preponderance of IEDs on one side may result in a better outcome postoperatively [23,24]. Chung *et al*. [23] evaluated whether or not the degree of lateralization of bilateral independent temporal IEDs is correlated with a good outcome (number of seizures in second postoperative year) in a group of 59 patients who underwent ATLR, 31 of whom also underwent intracranial monitoring with depth electrode recordings. Ninety-two per cent of patients with greater than 90% lateralization had a good surgical outcome compared with 50% of those patients who had less than 90% lateralization, even when all depth electrodes identified an ictal onset zone that was always ipsilateral to the side of resection.

Extratemporal interictal epileptiform discharges

Interictal epileptiform discharges are usually less useful for localization in extratemporal epilepsies than in mesial TLE. For example, unilateral frontal lobe epilepsy may produce unilateral, bilateral independent, bilateral synchronous (bifrontal) and generalized IEDs [21]. In a study by Laskowitz *et al*. [21], which included 16 patients with refractory frontal lobe epilepsy, the interictal and ictal scalp EEGs had a relatively poor sensitivity and specificity for the localization of the epileptogenic zone. Similarly, occipital lobe epilepsy can be associated with non-localizing and non-specific IEDs, including bilateral independent occipital IEDs, bilaterally synchronous frontal and occipital IEDs, and bilateral independent temporal (including anterior, mid and posterior) IEDs [18,25,26]. However, exceptional situations exist in which posterior epilepsies may manifest focal IEDs. Such patients may be better candidates for resective surgery. In a series published by Blume *et al*. [18], a principal interictal spike focus was present in 15 out of 19 (79%) patients who underwent a posterior corticectomy [18]. This IED focus correlated with the scalp or subdural ictal recordings in 14 patients and with clinical analysis and CT scan in one patient. Within this series, patients who had IEDs distant from the focus were less likely to achieve seizure freedom following surgery. Likewise, IEDs are rarely localized and more commonly diffuse or bilateral independent in parietal lobe epilepsy. Interictal scalp electroencephalography did not localize the epileptogenic lobe in 14 seizure-free patients in a study of patients with parietal lobe epilepsy by Kim *et al*. [20]. In four patients, IEDs were lateralized to the epileptogenic hemisphere, whereas they were non-lateralized in seven patients and were falsely localized to the frontal–temporal region in three patients. In many cases of extratemporal epilepsy, IEDs are non-localizing and, therefore, not typically useful in determining the epileptogenic region or predicting surgical outcome. However, Holmes *et al*. [27] reported that a strictly unifocal, interictal epileptiform pattern on scalp EEG in a minority of patients with refractory extratemporal partial seizures is predictive of ictal onset and successful postsurgical outcome.

Interictal non-epileptiform changes

Non-epileptiform focal changes also can be useful in determining the ictal onset zone, but such changes are not as well studied. Koutroumanidis *et al*. [28] reported that lateralized, polymorphic temporal delta activity had a lateralizing value similar to that of temporal IEDs in a group of 141 patients who had undergone temporal lobe resection and whose MRI was normal or showed mesial temporal lobe sclerosis. Interestingly, resections that were ipsilateral to the slowing were significantly more likely to have a favourable outcome, regardless of the laterality or topography of IEDs. This suggests that candidates with lateralizing temporal delta and normal MRI should not be barred from further preoperative assessment. Slowing that is temporal intermittent rhythmic delta activity (TIRDA) is also highly associated with TLE and has been reported to represent an epileptiform abnormality [29]. Gambardella *et al*. [29] found that TIRDA was highly lateralized in patients with unilateral mesial temporal sclerosis and also concordant with IEDs, but was not as well lateralized in patients with bilateral atrophy.

Interictal epileptiform discharges and excluding patients from presurgical evaluation

Interictal data have been suggested to be helpful in identifying patients who may not benefit from epilepsy surgery, thereby, excluding patients who are unlikely to proceed to surgery from inpatient evaluation. DellaBadia *et al*. [30] evaluated the predictive value of 2 h of interictal sleep-deprived EEG, MRI and PET in advance of inpatient EEG monitoring in a group of 69 patients, 35 of whom were offered resective epilepsy surgery; very few patients with normal EEG, MRI and PET [1 out of 13 patients (7.7%)] proceeded to surgery.

Ictal scalp EEG

Ictal patterns

The ictal onset zone identified with EEG provides a critical component of the testing battery necessary to plan epilepsy surgery and typically is analysed in the context of other structural and functional testing to define the resection's boundaries. Identifying the earliest portion of the EEG's ictal onset is necessary to maximize the accuracy of the ictal onset zone's localization, but this is difficult because EEG patterns during seizures vary considerably. The EEG pattern for partial seizures typically includes an evolution of the ictal rhythm in its frequency, amplitude, spatial distribution and morphology. Although the ictal signature of partial seizures varies, there are certain patterns that are more common in certain brain regions. For example, seizures originating from the mesial temporal region are often associated with the development of sinusoidal activity in the delta frequency range, which increases in frequency into the theta range with simultaneous development of phase reversals across the anterior temporal electrodes (F7/F8, T1/T2, S1/S2) followed by postictal delta slowing in the same region [31,32]. Risinger *et al*. [32] analysed

706 ictal EEGs from 110 patients who subsequently underwent intracranial depth electrode placement and found that the presence of a 5-Hz, or greater, unilateral temporal/sphenoidal rhythm within the first 30 s in 57 patients correctly predicted an ipsilateral temporal depth onset in 82% of cases. This predictive accuracy increased to 94% in the 33 patients whose ictal EEGs met this standard for all of their seizures. Seizures of lateral temporal onset may have an electrographic signature similar to those of mesial temporal onset, but typically show a lower mean frequency (2–5 Hz) of lateralized polymorphic rhythmic activity with a more hemispheric distribution [33]. Foldvary *et al*. [33] analysed 486 ictal EEGs in 72 patients with focal epilepsy from the mesial temporal, neocortical temporal, mesial frontal, dorsolateral frontal, parietal and occipital regions and found that surface ictal EEG was localized in 72% of cases, more often in temporal versus extratemporal cases, with 57% of localized onsets originating from the mesial temporal, lateral frontal and parietal lobe regions. Lateralized onsets were seen more frequently in neocortical TLE and generalized onsets were seen more frequently in mesial frontal lobe epilepsy and occipital lobe epilepsy, with more false localization/lateralization occurring in occipital and parietal seizures. In patients with mesial frontal lobe epilepsy, the ictal EEG is frequently obscured by muscle artefact or shows no abnormality [21]. Alternatively, if ictal changes are present, they often appear generalized and can be misleading [31].

Postictal EEG changes

In addition to ictal changes, postictal changes can also be instrumental in identifying the epileptogenic region. Postictal slowing or attenuation of normal rhythms is usually lateralized to side of ictal onset, although it can be falsely lateralized due to variable propagation. Lateralized postictal changes were present in 64% of recordings and concordant with the side of surgical resection in 96% in a study by Jan *et al*. [34], which evaluated postictal scalp EEG changes in 80 seizures from 29 patients with TLE.

Inter-rater reliability of ictal EEG

Given the range of patterns that can be seen on ictal EEG, interpretation of ictal EEG can be difficult, but the need for high inter-rater reliability is paramount. In a study of 144 ictal recordings of 54 patients who underwent scalp and depth electrode monitoring, Spencer *et al*. [35] found 58–60% agreement for lobe of seizure onset and 64–74% agreement for side of seizure onset on ictal scalp EEG. This agreement was greater for patients with TLE and less for patients with frontal lobe epilepsy. Inter-rater reliability was high, with 76–83% of seizures correctly lateralized in a study by Walczak *et al*. [36], which analysed 137 complex partial seizures (119 temporal and 18 extratemporal) from 35 patients who subsequently underwent resective epilepsy surgery and were seizure free for 2 or more years. This number improved to 93–99% when seizures with generalized features or those with obscuration of the record by artefact were excluded.

Limitations of scalp ictal EEG

Although the ictal EEG is an integral part of the presurgical evaluation, there are certain situations in which interpretation of the ictal scalp EEG is compromised to a clinically significant extent. First, scalp EEG typically does not show ictal discharges during simple partial seizures, even if the seizure produces bilateral movements (i.e. seizures from the supplementary motor area) [21]. Similar limitations may occur during a subset of complex partial seizures, particularly those arising from the mesial frontal lobe [21]. In cases of frontal lobe onset, or sometimes occipital lobe onset, the ictal EEG may show generalized spike–wave activity [31]. In some young children with focal brain lesions, generalized or multiregional interictal and ictal EEG abnormalities may be present [37]. However, these abnormalities do not necessarily preclude resective epilepsy surgery. Wyllie *et al*. [37] reported 50 paediatric patients, aged 0.2–24 years (median 7.7 years), with severe refractory epilepsy and a potentially epileptogenic lesion on brain MRI (congenital or early acquired), who underwent hemispherectomy (or lobar or multilobar resection) (see Chapter 73). Despite the observation that 30–100% of preoperative epileptiform discharges (interictal and/or ictal) were generalized or contralateral to the side of surgery, 72% patients were seizure free at the 24-month median follow-up, suggesting that the diffuse EEG abnormalities may reflect an interaction between the developing brain and an early lesion.

False lateralization: mesial temporal lobe epilepsy

Scalp ictal electroencephalography recordings sometimes provide false lateralizing information. In the case of mesial TLE, this false lateralization is typically secondary to rapid contralateral propagation, which is undetectable with scalp electroencephalography. Rates of false lateralization of ictal scalp electroencephalography have varied. Spencer *et al*. [35] reported the accuracy of scalp ictal EEG reading to be 21–38% for the lobe and 46–49% for the lateralization of seizure onset [35]. More recent reports have disagreed with this high incidence of false lateralization in the case of TLE. Alarcon *et al*. [38] found that 10.9% of seizures were falsely lateralized in a study of 314 seizures in 110 patients with TLE who underwent simultaneous scalp and foramen ovale ictal recordings. Additionally, in a retrospective study by Mintzer *et al*. [39], five patients with unilateral hippocampal atrophy and contralateral surface ictal recordings had depth electrode implantation that showed clear ictal onset in the mesial temporal lobe ipsilateral to the imaging abnormality in four of five patients and an unusual bitemporal onset pattern in one patient. It was interpreted that this ictal scalp pattern was secondary to severe hippocampal sclerosis or 'burned-out hippocampus', causing atypical depiction of ictal discharges.

False lateralization: lesional epilepsy

Falsely localizing or lateralizing information also can be seen on scalp ictal EEG in the case of lesional epilepsy. Sammaritano *et al*. [40] reported that scalp/sphenoidal EEG recordings showed ictal onset on the side contralateral to a known gross focal cerebral lesion that was acquired early in life in a group of three patients. These patients subsequently had implanted depth electrodes documenting onset ipsilateral to the lesion and then remained seizure free for 3–13 years postoperatively [40].

Williamson *et al*. [41] found that only 1 out of 11 patients with parietal lesions showed a focal EEG onset concordant with the parietal lesion, whereas 2 of the 11 patients showed an ictal onset ipsilateral to the lesion, and 8 of the 11 patients showed no focal changes at ictal onset. Despite the high rate of discordance between the side of lesion and the ictal onset, 10 of the patients underwent lesionectomy and all had a good outcome.

Late-appearing scalp ictal EEG

Sometimes scalp ictal electroencephalography changes appear late. Risinger *et al*. [32] analysed 706 ictal EEGs from 110 patients and found that 28 patients had one or more seizures with a focal 5-Hz (or greater) temporal rhythm that developed after the appearance of some other type of diffuse or ipsilateral electrographic change. In 22 out of the 28 cases, this delayed rhythm correctly predicted an ipsilateral temporal onset that was confirmed with depth electrode recordings. In one out of the six remaining patients the delayed focal pattern was falsely lateralizing, whereas in the other five cases the subsequent depth electrode monitoring did not show a unifocal temporal ictal onset. Nonetheless, the predictive accuracy of the initial focal pattern (≥5 Hz within 30 s) compared with the delayed focal pattern was not statistically significant. However, it is not known from this study whether or not delayed patterns predict a different seizure-free rate after resective surgery. Blume *et al*. [42] evaluated delayed ictal onset on scalp in a study of 52 consecutive patients at University Hospital, London, who became seizure free during 2 years of follow-up after temporal lobectomy. In total, 13 out of the 52 patients (25%) had a clear focal onset ipsilateral to the side of lobectomy, whereas 39 (75%) patients did not; late (≥5 s after hemispheric, diffuse or artefact obscured change) lateralizing or localizing features ipsilateral to the side of lobectomy were apparent in 37 out of 39 (95%) patients, and two (5%) patients had late contralateral and shifting features. The authors concluded that late lateralizing or localizing seizures are still valuable in establishing the laterality of temporal epileptogenic zones but should not be used in isolation. Supplementary clinical testing data should support the lateralization and provide a suspected localization.

Bilateral independent temporal ictal EEG

Scalp ictal EEG sometimes shows evidence of bilateral independent temporal ictal EEG changes, and this often requires subsequent intracranial electroencephalography for localization of a singular ictal onset zone. Holmes *et al*. [24] reported a study of 42 adults with bilateral independent temporal ictal onset on scalp EEG. In total, 26 (62%) out of 42 patients had unilateral ictal onsets on subsequent intracranial studies – 25 of these patients were offered resective surgery and subsequently underwent a tailored temporal resection; overall, 64% of these patients were seizure free postoperatively, whereas 12% had a >75% reduction in seizures when one of the following factors was concordant with the side of surgery: preponderance of interictal scalp EEG discharges, unilateral temporal lesion on MRI or lateralized mesial temporal memory dysfunction on neuropsychological testing. The seven patients who had bilateral independent intracranial ictal onsets subsequently underwent resection based on a preponderance of seizures on one side (>80%) or other lateralized non-invasive abnormalities, and five of these patients (those with >80% seizures from one side) had a >75% reduction in seizures postoperatively. It was therefore concluded that intracranial monitoring may benefit patients with bilateral independent temporal seizures when other non-intracranial assessments show evidence of lateralization. In a study by Jenssen *et al*. [43] 24 patients had evidence of bilateral independent temporal seizures on scalp EEG [43]. Twenty of these patients subsequently underwent intracranial monitoring, of whom 12 patients had localized ictal onsets, whereas eight did not. Sixteen patients subsequently underwent anterior temporal lobectomy and 13 out of 16 (81%) were seizure free. Lateralized findings on MRI and PET, a history of febrile convulsions and shorter duration of epilepsy were all associated with a focal onset on intracranial EEG, perhaps suggesting that intracranial monitoring is not always necessary in the setting of bilateral independent temporal seizures. Further studies are needed to clarify whether or not intracranial monitoring can be avoided in patients with bilateral independent temporal seizures on scalp EEG and evidence of lateralization on other non-intracranial assessments (see Chapter 62).

Scalp ictal EEG in non-lesional MRI

Despite its many limitations, scalp electroencephalography is an integral part of the presurgical evaluation and its role in patients with brain MRI-negative scans is paramount. Although the number of MRI-negative patients undergoing resective epilepsy surgery has decreased with the improved resolution of MRI, normal MRI is not rare. High-resolution MRI may fail to detect pathologies, including focal cortical dysgenesis, focal atrophy and gliosis (see Chapters 64 and 72). Although the lack of MRI abnormality does not preclude eventual resective epilepsy surgery, it does require additional diagnostic tests, which typically includes intracranial monitoring [44]. Scott *et al*. [45] reported that only 3 out of 40 non-lesional patients eventually proceeded to epilepsy surgery compared with 100 out of 182 who had MRI abnormalities, which demonstrates the value of MRI abnormality when considering epilepsy surgery [45]. However, a recent study by McGonigal *et al*. [46] reported no difference in the number of proposed surgeries between MRI-negative and lesional cases in a group of 100 consecutive patients who underwent intracranial monitoring. Regardless of the number of MRI-negative cases proceeding to surgery, scalp EEG studies are essential for planning intracranial monitoring studies, and implantation locations typically depend upon localizing data from other investigative studies. Hong *et al*. [47] reported ictal scalp EEG, interictal FDG-PET and ictal SPECT in a group of 41 patients with non-lesional neocortical epilepsy and found that all three tests provided equal lateralizing value; however, ictal EEG was most likely to depict a focal region concordant with the resection when surgery was successful. Moreover, 33 (81%) patients were seizure free or had a seizure reduction greater than 90% at a mean follow-up of 2.77 years. Sylaja *et al*. [48] reported a group of 17 patients with normal MRIs who underwent successful epilepsy surgery and found the following common features: the ictal EEG was a 5- to 9-Hz unilateral and/or subtemporal rhythm, the IEDs were concordant with the ictal lateralization and the patient had a

history of febrile seizures. Five patients (29%) were totally seizure free and an additional five patients had a greater than 75% reduction in seizure frequency.

Ictal behaviour: the role of video

The evaluation of presurgical candidates also includes a close study of the patient's seizure behaviour in conjunction with the ictal EEG. Ictal behaviour reflects the propagation of epileptic activity into eloquent cerebral areas and thereby represents the symptomatogenic zone [49]. In this regard, ictal behaviour improves lateralization and localization of the epileptogenic zone when used in conjunction with the ictal EEG, but it does not necessarily indicate the ictal onset zone or the epileptogenic zone. In a group of 55 patients with TLE, Marks and Laxer [50] found that unilateral clonic, dystonic and tonic activity were strong lateralizing signs of a contralateral epileptic focus, with a predictive value ranging between 86% and 100% [50]. Versive head rotation occurring less than 10 s before secondary generalization was predictive of a contralateral epileptic focus in all patients. Unilateral automatisms were predictive of an ipsilateral seizure focus in 80% of patients, whereas ictal speech preservation was indicative of seizure focus in the non-dominant hemisphere in 80%. Others have reported additional lateralizing ictal manifestations, including asymmetric visual, auditory or somatosensory auras, ictal spitting, vomiting, unilateral eye blinking, dysphasia, postictal hemiparesis, aphasia and nose-wiping (Table 61.1) [49]. Serles *et al*. [51] analysed the ictal scalp EEG recordings and clinical behaviour associated with 262 seizures recorded in 59 patients with TLE and found that ictal behaviour lateralized 46% of seizures and 78% of patients with a high degree of concordance with ictal scalp EEG lateralization. Moreover, the combination of ictal scalp EEG with ictal behaviour allowed for lateralization in a greater proportion of seizures (80%) and patients (95%) compared with each method alone. This combined lateralization was concordant with the side of operation in 33 out of 34 patients with a successful postoperative outcome (Engel class I/II).

Table 61.1 Lateralizing value of different ictal and postictal behaviours.

Sign	Side	Percentage
Aura		
Unilateral sensory aura	Contralateral	89
Hemifield visual aura	Contralateral	100
Motor		
Version (<10 s before generalization)	Contralateral	100
Clonic activity	Contralateral	83
Tonic activity	Contralateral	89
Unilateral dystonic posturing	Contralateral	100
Unilateral automatisms	Ipsilateral	80
Ictal spitting	Non-dominant	75
Ictal vomiting	Non-dominant	81
Unilateral eye-blinking	Ipsilateral	83
Language		
Ictal speech	Non-dominant	83
Ictal dysphasia and aphasia	Dominant	100
Postictal behaviour		
Postictal palsy	Contralateral	93
Postictal nose-wiping	Ipsilateral	92

Adapted from refs 49 and 50.

Psychogenic non-epileptic seizures

Close evaluation of ictal behaviour is also important for the diagnosis of patients with NESs, which is particularly important when considering patients for epilepsy surgery. NESs are seen in roughly 10–30% of patients who are referred to epilepsy centres for the evaluation of medically intractable seizures [52,53]. For example, Henry and Drury [53] unexpectedly recorded NESs in 12 patients (8%) referred for long-term monitoring for presurgical evaluation of medically intractable seizures who had interictal temporal spikes and reported ictal behaviour characteristic of temporal lobe seizures. Benbadis *et al*. [52] reported that NESs were diagnosed in 75 out of 251 (30%) inpatient video-EEG monitoring sessions of all patients (adults and children) who underwent inpatient video-EEG monitoring (≥24 h) at a university centre hospital over a 1-year time period. Conversely, some patients referred with suspected psychogenic non-epileptic seizures (PNESs) are found to have epileptic seizures. Referring physicians correctly suspected a diagnosis of epileptic seizures in 9 (43%) out of 21 patients, whereas 12 (57%) patients were incorrectly thought to have PNESs in a study by Parra *et al*. [54]. Ictal behaviour, in addition to history and electrophysiological data, helps to establish the diagnosis of NES. While there are no clinical manifestations that are entirely specific to PNESs, particular behaviours and patterns tend to be associated with PNESs more than with epileptic seizures. PNESs typically have longer durations, waxing and waning behaviours, and are less stereotyped in terms of behaviour and duration. Eye closure, especially when forced, and crying are much more common than in epileptic seizures.

Some behaviours may occur with similar features in both PNESs and epileptic seizures, which complicates the diagnosis and may lead to a misdiagnosis of epilepsy as PNESs as easily as PNESs as epilepsy. Both PNESs and frontal lobe epileptic seizures may include screaming, violent thrashing of the extremities or whole body, opisthotonic arching of the back, side-to-side head movement and bilaterally out-of-phase clonic jerking [55]. The out-of-phase movements may resemble kicking or pedalling. Seizures originating in the supplementary sensory motor cortex may present with preserved consciousness despite bilateral tonic posturing, both of which may be misinterpreted as behaviours suggestive of PNESs. This similarity is demonstrated by the observation by Kanner *et al*. [56] that clinical behaviours suggestive of PNESs were present in 82% of all seizures recorded from 91% of the studied patients with frontal lobe epilepsy.

Although a diagnosis of additional psychogenic seizures in patients with medically intractable surgically remediable epileptic seizures should not be considered an absolute contraindication to surgery, identification of the PNESs is important for careful preoperative psychiatric evaluation [57]. Ultimately, the evaluation of ictal behaviour is an important component of the presurgical evaluation, and when used in conjunction with the EEG, neuro-

imaging, functional mapping and neuropsychological testing it can help to estimate the epileptogenic zone and adapt surgical intervention.

Seizure activation during long-term monitoring

Because of the nature of epilepsy, seizures are usually unpredictable, may not have an obvious trigger, and occur sufficiently infrequently that several days or more of video-EEG monitoring are required. Most epilepsy surgery programmes require the recording of three to five independent seizures in order to formulate a surgical decision [58]. The number of seizures ultimately depends upon whether or not the recorded seizures have a stereotyped pattern. Todorov *et al*. [59] found that the mean length of stay was 2.9–3.7 days to record one seizure. To record three seizures was 4.5–5.5 days and to record five seizures was 6.1–7.6 days. Given the expense of long-term monitoring, activation procedures are routinely used to shorten the length of stay and thereby improve cost-effectiveness and efficient use of this medical resource.

Antiepileptic drug withdrawal

A facilitative procedure that is commonly used during long-term monitoring is antiepileptic drug (AED) withdrawal. Although some patients (particularly those with extratemporal partial seizures) may need minimal reduction of AEDs to capture a sufficient sample of seizures, many patients (particularly those with temporal lobe seizures) commonly require a large reduction in AEDs to record an adequate number of seizures in a reasonable period of time [60]. The rate and order of AED withdrawal is determined by the clinical judgement of the treating physician and is largely contingent on a patient's baseline seizure frequency at home and his/her tendency to have generalized seizures or status epilepticus. The taper for some patients may be started before admission, particularly if the patient provides history that the medication has not been helpful or if medication levels are low. Typically, physicians taper AEDs by one-quarter to one-half of the maintenance dose every day. Some taper all AEDs simultaneously, based on the observation that increased seizure frequency may be delayed for weeks if other AEDs are continued [61]. Our practice has been to taper the AEDs individually by about one-third of the dose in order to maximize both safety and the quality of the ictal onset recordings. Slower tapers decrease the likelihood of seizures that are more severe than the patient's usual, and produce an ictal spread on the EEG that is too quick to clearly depict a focal onset region. There is controversy as to whether seizure activation occurs when the anticonvulsant levels are falling [62] or when the levels reach a threshold low value [61,63]. Abrupt discontinuation of barbiturates [64] and benzodiazepines [65] can result in withdrawal seizures, even in those without epilepsy. In a study of patients with complex partial seizures who were withdrawing from phenobarbital, Theodore *et al*. [66] found that seizure rates were highest when high serum concentrations fell below 15 μg/mL.

Regardless of the mechanisms of increased seizure frequency with AED tapering, there has been concern that seizures observed during this activation may originate from ictal foci different from those producing a patient's habitual seizures [62,67]. However, the significance of these case reports is uncertain. Subsequent studies have shown that the origin of seizures during AED tapering does not change as long as seizures have behavioural features identical to the habitual seizures [63]. AED tapering has been shown to result in increased frequency of complex partial seizures, seizure clusters and an increased frequency of secondarily generalized seizures [60,63,68]. Yen *et al*. [63] reported a series of 102 consecutive patients with refractory TLE who were admitted for presurgical evaluation in whom AEDs were rapidly decreased and discontinued within 4–6 days. Eighty-nine patients had 429 complex partial seizures (mean of 4.8 per patient), including 156 (36%) that secondarily generalized, whereas 43 (48%) patients had seizure clusters and eight patients (9%) had generalized seizures that had not occurred or been absent for years. Swick *et al*. [60] reported that the only significant predictor of secondarily generalized seizures during monitoring was a history of such activity at home in patients with temporal lobe seizures (versus extratemporal seizures). Although rare during monitoring, status epilepticus may occur and this risk is a factor when planning the tapering [68]. AED tapering also may result in an increased risk of seizure clustering [63]. Haut *et al*. [69] found that risk factors for seizure clustering (defined as ≥3 seizures in 24 h) during long-term monitoring included a history of clustering at home, MRI evidence of mesial temporal sclerosis and multiple seizures types. In this study, however, seizure clustering was not associated with ictal localization or AED withdrawal, suggesting that clustered seizures are useful in identifying the epileptogenic zone [69].

Sleep deprivation

Sleep deprivation is another method employed to facilitate seizures during long-term monitoring. This method is based on the premise that many epilepsy patients report seizure exacerbation, or precipitation, with sleep deprivation [70]. In a study by Rajna and Veres [71] the likelihood of occurrence of a seizure was significantly higher after a period of partial sleep deprivation than in normal sleep or oversleep in a group of 14 patients with TLE. Sleep deprivation also activates IEDs [72]. As such, many epilepsy centres utilize sleep deprivation protocols. However, Malow *et al*. [73] found that sleep deprivation every other night did not affect seizure frequency during inpatient monitoring in a group of patients with medically intractable seizures who were undergoing inpatient monitoring. Overall, sleep deprivation often does not facilitate seizures but its occasional utility makes it a worthwhile procedure in some clinical circumstances.

Hyperventilation

Hyperventilation is an activation method that is less commonly employed in the presurgical evaluation. This is partly due to this method's greater specificity to EEG abnormalities of idiopathic generalized epilepsies than to those of focal epilepsies. Holmes *et al*. [74] reported that hyperventilation activated seizures in only 0.5% of 384 patents with partial epilepsy who were

undergoing routine outpatient EEG testing. Although some have reported an increase in interictal discharges and seizures during hyperventilation in patients with complex partial seizures, especially prolonged hyperventilation, others have not found this to be the case. More specifically, Miley and Forster [75] found that hyperventilation increased the frequency of interictal discharges and activated seizures (6% and 4% respectively) in 255 patients with complex partial seizures. In contrast, Guaranha *et al*. [76] found that hyperventilation activated focal seizures in 25% of 97 patients with medically intractable partial epilepsy when performed every 3 h, with temporal lobe epilepsies significantly more activated than frontal lobe epilepsies.

Photic stimulation

Photic stimulation can also be used to activate seizures. Photosensitivity typically does not occur in patients with partial seizure disorders, although it may activate focal occipital spikes. Such sensitivity is uncommon and typically occurs in patients with a history of a lesion in the occipital cortex [77] and a more anterior lesion in rare circumstances [78]. Most people with photosensitivity have idiopathic generalized epilepsy, and if a seizure is elicited it is typically a primary generalized tonic–clonic seizure, an absence seizure or a myoclonic seizure.

Potential complications

Although several activating techniques can be used to provoke seizures and reduce the duration of video-EEG monitoring, safety is of paramount importance as complications can occur during inpatient monitoring. Up to 50% of patients have secondarily generalized seizures during monitoring, many of whom rarely generalize at home, and many patients experience seizure clustering [63,68]. Prolonged or recurrent seizures can lead to a variety of complications including aggressive postictal behaviour and psychosis [79] and an increased risk of status epilepticus [80]. Whether occurring in clusters or isolation, seizures, particularly secondarily generalized, can result in falls leading to potential fractures, joint dislocations or soft tissue injuries [68]. Although status epilepticus is a rare complication, occurring in 3% of patients admitted for video-EEG monitoring [68], it is associated with numerable potential serious complications, including metabolic derangement, infections (such as aspiration pneumonia and sepsis), autonomic instability, renal failure and death. Given the nature and range of possible complications, safety precautions, including a well-trained staff, intravenous access, and continuous observation of patients, should be taken [81].

Conclusion

Scalp EEG is a fundamental test in the presurgical evaluation of patients with medically refractory epilepsy who are being considered for resective epilepsy surgery. Evaluation of interictal and ictal scalp EEG patterns and corresponding ictal behaviour are critical steps in the identification of the epileptogenic zone. As structural MRI resolution continues to improve, the results of video-scalp EEG monitoring contribute to the determination of whether or not the identified structural abnormalities are likely to be epileptic. In this regard, the results shown by the scalp EEG are commonly used in direct conjunction with structural MRI in order to formulate a plan for resective epilepsy surgery or alternatively intracranial electroencephalography monitoring.

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63 MEG in Presurgical Evaluation of Epilepsy

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Introduction

Epilepsy surgery primarily aims to control seizures in pharmacoresistant epilepsies; in addition, neurological or neuropsychological deficits should be avoided and social integration improved. Before imaging techniques became increasingly important, for a long time electroencephalography had been the only functional investigation technique for presurgical evaluation. The individual determination of the localization and extent of interictal (irritative) and ictal epileptic (seizure onset) brain regions is the main task during presurgical evaluation of partial epilepsies. Another important issue concerns the delineation of functionally important areas (e.g. motor, somatosensory, language). Therefore, functionally important areas have to be correlated with the localization of epileptogenic areas.

As neurosurgical approaches have become routine procedures in the treatment of pharmacoresistant focal epilepsies, the diagnostic challenge culminates in determining the site and extent of epileptogenic tissue to be removed without risk of functional deficits. To this purpose, the combined findings of diagnostic methods may contribute anatomical (CT, MRI), blood flow [single photon emission computerized tomography (SPECT)], metabolism-related [positron emission tomography (PET)] and electrophysiological information. This information comprises long-established non-invasive surface electroencephalography and invasive electroencephalography recordings and, as a comparatively new method, magnetoencephalography (MEG). MEG is a non-invasive method with high temporal and potentially high spatial resolution, offering data on electrophysiological phenomena from a point of view that is somewhat different to that of the electroencephalogram (EEG), and has been found to be a potentially useful addition to the pool of techniques that are applied in preoperative focus localization of pharmacologically intractable epilepsies. As the standard procedure for MEG processing includes coregistration with MRI, centres of activity localized from MEG data are usually displayed in the corresponding anatomical images. This particularly advantageous combined technique [1,2] has been labelled 'magnetic source imaging' (MSI).

Epileptic activity can be generated both in superficial cortex and in deeper brain regions, thus influencing detectability [3]. The feasibility of localization has to be considered for any given type of focal epilepsy (neocortical or limbic). Basically, a certain amount of cortex has to be involved by epileptic discharges to be accessible non-invasively [4–7]. Therefore, presurgical evaluation requires extensive experience in deciding whether or not non-invasive interictal or ictal recordings are sufficient for the localization of focal epileptic activity in any individual case, or if invasive recordings have to be carried out in order to improve the accuracy of preliminary non-invasive results. For instance, if the generator is located in the hippocampus then non-invasive detection of epileptic activity may be difficult or impossible. The distribution of interictal spikes in deep hippocampal electrodes and surface electrodes was analysed by Alarcon *et al.* [4]. The results of this study indicate that single hippocampal discharges could not always be detected by scalp EEG, but excision of 'leading regions of spike activity' in the temporal lobe yielded good surgical outcome [8].

According to our experience with simultaneous invasive recordings from hippocampus, temporal basal, mesial temporal and temporal neocortical areas in many patients with cryptogenic temporal lobe epilepsies, hippocampal and parahippocampal or basal areas or inferior temporal gyrus are involved in the epileptic aggregate. Rather frequently we observed spike onset in the entorhinal, parahippocampal cortex and sometimes in the lateral neocortex [8]. Invasive ictal recordings revealed that the entorhinal cortex of the basal temporal cortex itself can be the region of ictal onset [9]. Thus, it may happen that the hippocampus is only secondarily involved in the epileptic excitation process. The epileptic network in such an instant involves temporomesiobasal areas as well as the hippocampus.

As discharges involving only several thousands of neurones are assessable non-invasively, only approximated localizations within the neuronal network of the brain are possible. The question arises if magnetoelectroencephalography is able to define 'critical hot spots' in the neuronal network, which are necessary and sufficient for seizure generation and control. In this chapter, procedures and applications of MSI in epileptic patients for the detection of focal epileptic interictal and ictal activity and functionally important areas are discussed.

Method

It is well known that activated groups of neurones in the human brain produce electrical potentials that can be recorded with scalp electroencephalography. At the same time, the neuronal activity also produces very small magnetic fields outside the head in the range of 50–1000 femtotesla (fT), which can be detected by MEG. Special sensors [superconducting quantum interferometer devices

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(SQUIDs)] are essential for the assessment of these small magnetic fields. In addition, MEG recording is usually performed in a specific shielding chamber to attenuate the influence of external magnetic noise. For technical details about registration and instrumentation of MEG, see refs 10–13.

Magnetoencephalography is a non-invasive method requiring neither referencing nor direct contact between the recording equipment and the patient's head. Its high temporal resolution in the milliseconds range is similar to that of the EEG. Owing to the use of multichannel systems, and particularly the so-called whole-head systems with up to more than 200 sensors, good spatial resolution has also been achieved.

The so-called neuromagnetic 'inverse problem' – the tracing of an unknown source in the brain from magnetic field data recorded outside the head – is approached using special model assumptions concerning the type of underlying source that produces the magnetic field and the shape and structure of the volume conductor. For the determination of the location, orientation and strength of focal activity in the brain, the model of a single equivalent current dipole is often used (with a specific physical feature of magnetic field recording being its 'blindness' to radial portions of the dipoles). However, when sources overlap both spatially and temporally (i.e. in the case of multifocal sources and extended networks) the approach of a multidipole model might be more appropriate [14–16]. Furthermore, different current density reconstruction approaches, e.g. minimum norm, weighted minimum norm and low-resolution brain electromagnetic tomography (LORETA) [17,18] and beamformer methods [19], are also used for the localization of more extended generators.

As to the volume conductor, besides the most frequently used spherical model, more realistically shaped models are also available [e.g. boundary element method (BEM)]. In this case, the volume conductor model consists of the three different compartments – brain, skull and skin – assuming that each compartment has homogeneous and isotropic conductivity [20]. The BEM is based upon segmentation of MRI datasets, thus accounting for the individual patient's anatomy. This is taken further by finite element models (FEMs), which also take conductivity anisotropies into account [21].

Clinical aspects of MEG methodology have been presented in the work of Stefan and Hummel [22].

Applications of magnetic source imaging in epileptic patients

Evoked activity

When neurosurgery remains the only therapeutic hope for epileptic patients, it is essential to know not only the site of the epileptogenic region (see below), but also whether or not removal of the tissue in question may cause functional deficits.

Recently, functional validation of MSI has been obtained with various sensory modalities, source localization being based upon evoked magnetic responses to repeated stimulation, in accordance with the well-established technique for evoked potentials, averaged over a number of stimulus-related electroencephalography epochs [23].

Evoked magnetic responses to acoustic [auditory evoked field (AEF)] [24,25], visual [visual evoked field (VEF)] [26–28], somatosensory [somatosensory evoked field (SEF)] [29] and olfactory [olfactory evoked field (OEF)] [30] stimulation can be obtained. Magnetic fields representing motor activity [motor evoked fields (MEFs)] generated by voluntary finger and limb movements have long been assessed [31–33]. Thus, localization of cortical generators calculated from magnetic evoked activity has become an established tool to provide information about functionally significant areas, and particularly so if MSI and neurosurgery have access to compatible systems of space coordinates ('neuronavigation' systems are already established in operation theatres – see Plate 63.1). Using a variety of stimulating sites, SEF localizations illustrate the 'homuncular' organization and its variations of the somatosensory cortex [22,34,35]. It is also possible to localize functional regions for language [36–38].

Spontaneous activity

An increasing number of publications are dealing with the application of MEG in presurgical evaluation, giving evidence of its capability to localize spontaneous epileptic activity (Plate 63.1).

Validation of source localizations with respect to the 'true' source is necessary. MEG findings on epileptogenic foci need to be compared with the results of other diagnostic techniques that are considered to be the most reliable in detecting the epileptogenic brain tissue. Whether ictal invasive electroencephalography (widely considered to be the 'gold standard' [39]), long-term video electroencephalography monitoring or intraoperative electrocorticography (EcoG) is wanted to check the accuracy of MEG focus, localization, depending on other clinical findings, has to be decided upon in each individual case. It has been shown that MEG indeed yields fairly good accuracy, even although the activity investigated is mostly interictal [40–47].

Eliashiv *et al.* [48] reported congruency of MEG localizations with other findings of presurgical evaluation in 70–80% of cases. We found a similar percentage (72%) of patients after successful temporal lobe epilepsy surgery with good spatial correlation between predominant focal epileptic activity in MEG and other localization results from presurgical evaluation and intraoperative EcoG [49]. In another study, a comparison of MEG localizations with MRI and various video electroencephalography findings in 58 patients with pharmacologically intractable epilepsy showed that in patients who, after surgery, were seizure free (class I, according to Engel's classification) or had only rare seizures, MEG was inferior to only subdural video electroencephalography recordings in predicting the epileptogenic zone. MEG was superior to MRI, interictal and ictal non-invasive video electroencephalography and interictal invasive subdural electroencephalography [50]. The data suggest that MEG is at least as effective as the established methods for localizing the epileptogenic network in temporal and extratemporal lobe epilepsies. In a study comparing MEG with PET and stereoelectroencephalography (SEEG), MEG localizations agreed with PET and SEEG results in seven out of nine patients. If PET and MEG findings agreed, the outcome after surgery was favourable [51].

King *et al.* [52] reported outcome data (according to Engel's classification) in 19 patients after resection of the primary MEG spike region: 14 patients were grouped in class I, four in class II, one was in class III and none in class IV. On the other hand,

out of 17 patients after resection of tissue with marginal or no relationship to MEG spike localization, only three were in each of the best and second-best outcome category, whereas in four cases the outcome ranked in class III and a major portion of seven cases were graded in the worst outcome class.

These results indicate that resection of the primary MEG spike focus correlates strongly with excellent outcome. In this context, it seems important to note that MSI dipole localizations are considered neither to represent point-shaped sources with millimetre accuracy nor to yield an outline of the epileptogenic tissue, but rather to indicate centres of epileptic activity, revealing compartmental information on a sublobar level. In many patients with pharmacoresistant focal epilepsies, circumscribed clusters of localizations, indicating centres of predominant epileptic activity, can be found [53]. If MEG localizations in temporal lobe epilepsy showed more than one distinct cluster in different regions, this was interpreted as a hint towards multifocal temporal lobe epilepsy. Similar results were found for neocortical extratemporal epilepsies [54].

Although, in many cases, cerebral MRI of epileptic patients shows abnormal morphology, varying from subtle alterations to extensive mass lesions, abnormal MRI findings are not necessarily epileptogenic and, even if so, it may be important to clarify the relation between anatomical and functional pathology in detail. Furthermore, if there is more than one lesion, those crucial to epileptogenicity must be determined. In a considerable number of patients with neocortical temporal or extratemporal epilepsies, MSI yielded localizations of epileptiform activity in proximity to an epileptogenic structural lesion [42,55–57].

On the other hand, before surgery there is sometimes no evidence of morphological pathology associated with epilepsy [58,59]. However, with the availability of new powerful imaging systems, and more sophisticated software to identify discrete alterations, the number of patients with 'cryptogenic' aetiology is decreasing, and it is not yet possible to identify a structural abnormality to account for any epileptic focus. The lack of morphological clues renders the functional diagnostic methods more significant and even enables detection of subtle morphological changes in MRI re-evaluation [60]. MSI has been found to offer useful source locations of cryptogenic epileptic activity in accordance with other non-invasive results, thus facilitating the detailed planning of invasive procedures and neurosurgical regimen. In a study by Knowlton *et al.* [55], in 11 out of 12 patients without focal abnormality on MRI, MEG discharges were localized to the epileptogenic zone as determined by standard preoperative evaluation.

A review carried out by King *et al.* [52] found numerous studies showing that MEG can detect interictal epileptiform discharges in patients with intractable epilepsies. However, there are cases in which MEG spike localization does not result in focal source findings.

A major problem in using MEG for focus localization arises from the fact that sources of spontaneous epileptic activity are often located less superficially than, for example, the comparatively easily accessible cortical generators of evoked responses. As the signals recorded at the surface decline drastically with increasing depth of the source, deep sources are more difficult to locate than superficial ones. A crucial question in the management of drug-resistant epilepsy is the capacity of magnetic field recordings of spontaneous brain activity to assess deep sources in the mesial structures of the temporal lobe. Initial attempts have been made to resolve this issue. In an unpublished study in which experimental dipoles were established at the tips of foramen ovale electrodes, we found that the dipoles were localized in deeper parts of temporal brain regions, with the distance between estimated source and experimental dipole ranging from 8 to 22 mm. This result gives some encouragement to the use of MSI localizations for presumed deep epileptic foci. However, the circular arrangement of cell layers, for example in the amygdala, may cause cancellation of magnetic fields, thus jeopardizing detection of the signals. In addition, an unfavourable sensor configuration may also impair sensitivity. Smith *et al.* [61], comparing MEG localization with 'standard localizations' (based upon MRI, non-invasive and invasive electroencephalography) found agreement in about two-thirds, with spontaneous spikes available in approximately one-half of the the mesial temporal lobe epilepsy (MTLE) cases. Knowlton *et al.* [55] confirmed that the yield of MEG is higher in patients with neocortical epilepsies than in those with MTLE.

A frequently used measure to increase the signal–noise ratio when dealing with small amplitudes of epileptic discharges in patients with foci in deeper brain regions is the averaging of similar specific patterns. When subjected to spatiotemporal analysis, the resulting signals are more likely to produce a reliable estimate of focal epileptic activity than the unaveraged data [62,63].

Based primarily on dipole analyses of EEG spikes, Ebersole *et al.* [40] stressed the usefulness of interpreting dipole orientation in order to obtain additional information about sublobar attribution of localizations in the temporal lobe and this technique was also described by Pataraia *et al.* [64].

A further difficulty for source localization lies in the epileptogenic network itself. Although the concept of a circumscribed epileptic focus is a valid and useful hypothesis for most patients with focal epilepsies, some patients present with complex signals that challenge the simplicity of this model. In these, the histological cause of epilepsy is better described in terms of interconnected networks with distinct and extended components. Source localization then faces the challenge of modelling this complex structure to explain observed signals.

Owing to the distribution of focal origins of seizure disorders, early clinical MSI studies in epileptic patients were mostly restricted to temporal lobe cases [40,42,62,64–66]. Nevertheless, presurgical evaluation of patients with extratemporal epilepsies has also been reported to benefit from MSI [22,67–71]. In frontal and other extratemporal epilepsies, intralobar localizations (predominantly lateral and frontobasal) could be confirmed by invasive recordings, but until now the number of investigated patients is rather small. Plate 63.1 gives an example of localization results in a patient with frontal lobe epilepsy. A special challenge in frontal lobe cases is propagation analysis [72].

The newer generations of biomagnetic systems, allowing for simultaneous examination of large fields of interest (both hemispheres or the entire head), are particularly suited for the investigation of epileptic spikes [73,73] as they offer the opportunity to investigate temporal relationships of events with extended spatial distribution, for example mirror foci [68].

Owing to relatively short MEG recording times (compared with long-term electroencephalography monitoring), spikes are not detected in all patients with focal epilepsy. The rate of MEG spike detection in focal epilepsies varies between 70% and 90% of spontaneous spikes. In order to induce more frequent spiking, activation using methohexital and/or clonidine can be used [74,75].

Furthermore, with limited recording duration, most MEG recordings miss ictal activity, even in inpatients whose antiepileptic medication is reduced for presurgical evaluation purposes. The restricted access to ictal recording presently remains one of the basic problems of MSI. Even if ictal activity is obtained, it is known from electroencephalography that motor artefacts are likely to disturb the brain signals. Yet, MEG data recorded during auras or seizure onset [40,44,49, 76–78] may yield dipole localizations reflecting focal activity (Plate 63.2). According to investigations by Ebersole *et al*. [40] and Tilz *et al*. [79], ictal recordings permitted the detection of epileptiform signals in the MEG in 40–50% of cases. Prolonged MEG recordings, split into repeated sessions and interspersed with breaks for the patient to have a stretch, might be a strategy to provide ictal data during spontaneous seizures. Another way to obtain seizure-related MEG measurements is to take advantage of procedures that provoke the attacks. For seizure precipitation, sleep deprivation and antiepileptic drug (AED) withdrawal can be used.

The correlation of ictal and interictal localizations is among the important issues that have to be assessed systematically in future research in different types of epilepsies.

In small children, limited cooperation and small head size may impose limitations on recording and analysis. Still, even under these conditions, MEG proved advantageous. In childhood epilepsy with Landau–Kleffner syndrome, Paetau *et al*. [80], using a whole-head system, showed that in all investigated patients the earliest spike activity originated in the intrasylvian cortex. In one subject, activity spread to the contralateral sylvian cortex within 20 ms. Secondary spikes occurred within 10–60 ms in the ipsilateral perisylvian temporo-occipital and parieto-occipital areas. In these cases, MEG provided useful presurgical information regarding cortical spike dynamics.

Studies comprising MEG and electroencephalography data recorded and analysed simultaneously [65,81,82] are of particular interest, enabling clinicians to take full advantage of the merits of both methods and to overcome their drawbacks.

Despite the specific limitations of the MSI technique – MEG being apt to detect only tangential components of dipoles and the comparatively short recording periods rendering spontaneous ictal recordings unlikely – the advantages of MSI are undeniable. Its non-invasiveness, high spatial and temporal resolution, superior accuracy due to magnetic fields' independence of conductivities and its merging functional and anatomical information suggest that MSI plays a significant role among the diagnostic methods that contribute to finding epileptic networks. Being non-invasive, MSI is restricted neither to inpatients nor to presurgical evaluation, and is also applicable to projects screening outpatients. It may be particularly useful in patients in whom, post operation, seizures have decreased but have not altogether ceased and when, due to asymmetrical conductivities, the defect of the cranial vault and the cavity resulting after resection impede electroencephalography but not MEG analysis.

The applications of MSI in presurgical epilepsy evaluation can be summarized as follows:

- delineation of functionally significant areas (which must be spared in neurosurgery) by means of evoked activity (Plate 63.3);
- localization of epileptic activity to guide invasive procedures and thus reduce invasive regimens;
- localization of epileptic activity to guide detailed planning of neurosurgical procedures, for example with neuronavigation, aiming at the removal of as little tissue as possible;
- contribution to elucidating spatial relationships of epileptic spike generation and (even subtle) anatomical pathologies;
- postoperative follow-up and facilitation of the decision concerning the possibility of a second operation in cases when the first neurosurgical treatment has failed to render the patient seizure free.

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64 MRI in the Presurgical Evaluation

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Introduction

The development of high-resolution MRI has noticeably modified the presurgical evaluation of pharmacoresistant epilepsies over the last decade. While previously electrophysiological focus localization was the primary diagnostic tool, today MRI can be regarded as the entrance criterion to a successful presurgical evaluation. On the one hand, it may help to identify good surgical candidates. On the other hand, detecting inoperable lesions can avert complex and risky work-ups and futile resections without a realistic chance of seizure freedom and can reduce superfluous health-care costs. Today's role of MRI is established on the experience that surgery is most effective when an epileptogenic lesion can be identified preoperatively and completely removed [1]. Owing to the constant improvements in MRI technology, now even subtle epileptogenic lesions can be detected.

The importance of MRI in epilepsy surgery is underlined by the fact that during the course of the disease, it helps define the time at which the patient should be considered a surgical candidate. The classical route to epilepsy surgery assessment required 'proven pharmacoresistance'. However, the concept of pharmacoresistance was and still is controversial [2]. Many patients are exposed to a multitude of anticonvulsive drugs and after approximately 20 years they are finally identified as good surgical candidates [3]. For a good surgical candidate, 20 years of seizures are lost years.

Because the chance of achieving seizure freedom through medication after the first drugs have failed is fairly low [4–6], patients with easily accessible epileptogenic lesions should be considered for a surgical treatment early on. Patients with lesions that are not well suited for surgery, or who do not show lesions on MRI, should undergo surgical treatment only after more extensive pharmacotherapy. In other words, pharmacoresistance should be defined individually, based on MRI (Table 64.1).

However, the lesion-oriented definition of individual pharmacoresistance requires high-quality MRI assessment during the early stages of the disease. Surgery is delayed for many patients considered difficult surgical candidates simply because of insufficient MRI performance, evaluation and/or judgement [7].

In this chapter, we outline the MRI requirements for the effective identification of surgical candidates and describe the role of MRI in the presurgical evaluation. We illustrate a system of patient classification by providing exemplary cases of 'easy', 'moderately difficult', 'very difficult', palliative and 'non-surgical' candidates. We also discuss the role of MRI postprocessing for patients with non-lesional MRI. We address MR-based auxiliary techniques such as MR-volumetry, MR-relaxometry, functional MRI (fMRI) and diffusion-based imaging. Finally, we address the usefulness of combining multiple imaging techniques, including multimodality neuronavigation.

Structural imaging

Timing of MRI examination and technical requirements

Focal epilepsy can manifest itself at any age and seizure aetiologies are highly heterogeneous. Accordingly, MRI of patients with focal epilepsy can reveal many different lesions [8]. Except for emergency situations and in rare patients with calcified lesions in whom CT scans are advantageous (better accessibility, shorter examination time, fewer contraindications, etc.), MRI offers much better chances of identifying the causes of newly manifested seizures. Because different seizure aetiologies require principally different therapies (e.g. neoplasm versus encephalitis versus malformations), it is generally agreed that each epilepsy patient should undergo diagnostic MRI as early as possible.

However, it is the quality of MRI which determines if lesions can be detected. Large lesions can be identified even on a low-quality MRI and by a radiologist who is not experienced in the evaluation of epilepsy patients. The poorer the MRI performance, evaluation or judgement is, the higher the danger of overlooking epileptogenic lesions [7]. This may be problematic particularly for patients with subtle yet highly epileptogenic lesions such as focal cortical dysplasia (FCD). Once the diagnosis 'non-lesional' is fixed in the charts, it can persist for years and the patient may be categorized as a bad surgical candidate for a long time despite having an excellent chance of achieving seizure freedom through resective surgery.

In most countries, 1.5-tesla MRI (1.5-T MRI) is the standard and most publications on epilepsy surgery strategies and outcomes rely on magnetic resonance images that are acquired at this magnetic field strength. Therefore, for the purposes of diagnosing and treating epilepsy, MRI with field strength of less than 1.5 tesla should no longer be performed. Today, 3-tesla MRI (3-T MRI) is widely available. By using higher magnetic field strength, examinations can be performed at higher resolution and with higher signal-to-noise ratio in less time [9,10]. In particular, the contrast of grey and white matter and the resolution of the internal struc-

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Table 64.1 Individual definition of pharmacoresistance depending on (1) the expected chance of seizure freedom; (2) the degree of difficulty of presurgical evaluation; and (3) the risk of neurological deficits through epilepsy surgery.

Candidate classification	Timing of surgery
A: *Easy candidates* Very high chance of seizure freedom through surgery (≈80%) Low risk of neurological/neuropsychological deficits	Early
B: *Moderately difficult candidates* High chance of seizure freedom (≈60%) Complicated (invasive) presurgical evaluation and/or some risk of neurological/neuropsychological deficits	Later
C: *Very difficult candidates* Reduced chance of seizure freedom (<50%) Significant risk or certainty of neurological/ neuropsychological deficits	Late
D: *Palliative surgery candidates* Chance of seizure freedom only for seizure subtypes	Late
E: *Non-surgical candidates* No realistic chance of seizure freedom Surgery impossible without intolerable neurological deficits	–

ture of the hippocampus is much better at 3 T (Fig. 64.1). Although the superiority of 3 T over 1.5 T has not yet been formally proven with respect to surgical outcome, centres working with 3 T report a much higher level of confidence when using this technique.

Yet because of the high incidence of epilepsy, not all patients can receive an initial 3-T MRI scan. For logistical reasons, and to avoid unnecessary costs, it is reasonable to perform initial 1.5-T MRI after seizure onset. If no typically epileptogenic lesion that is consistent with the epilepsy syndrome is found but the seizures prove difficult to control by pharmacotherapy then 3-T-MRI should be performed.

Regardless of the field strength, MRI undergoes constant improvement. New sequences that promise higher sensitivity for lesions are developed and introduced into clinical application. This means that in pharmacoresistant, non-lesional patients in whom epilepsy surgery might be considered, repeated 1.5-T MRI examinations can make sense, too. We usually recommend repeating an MRI every 4–5 years if from the improved technology a clinical yield can be expected. Table 64.2 summarizes the recommendations for a staged performance of cranial computerized tomography (CCT), 1.5-T MRI and 3-T MRI.

Because of the superior quality and the trend towards wider distribution of 3-T MRI, all of the MRI examples shown in this chapter are 3-T MRI (unless otherwise stated).

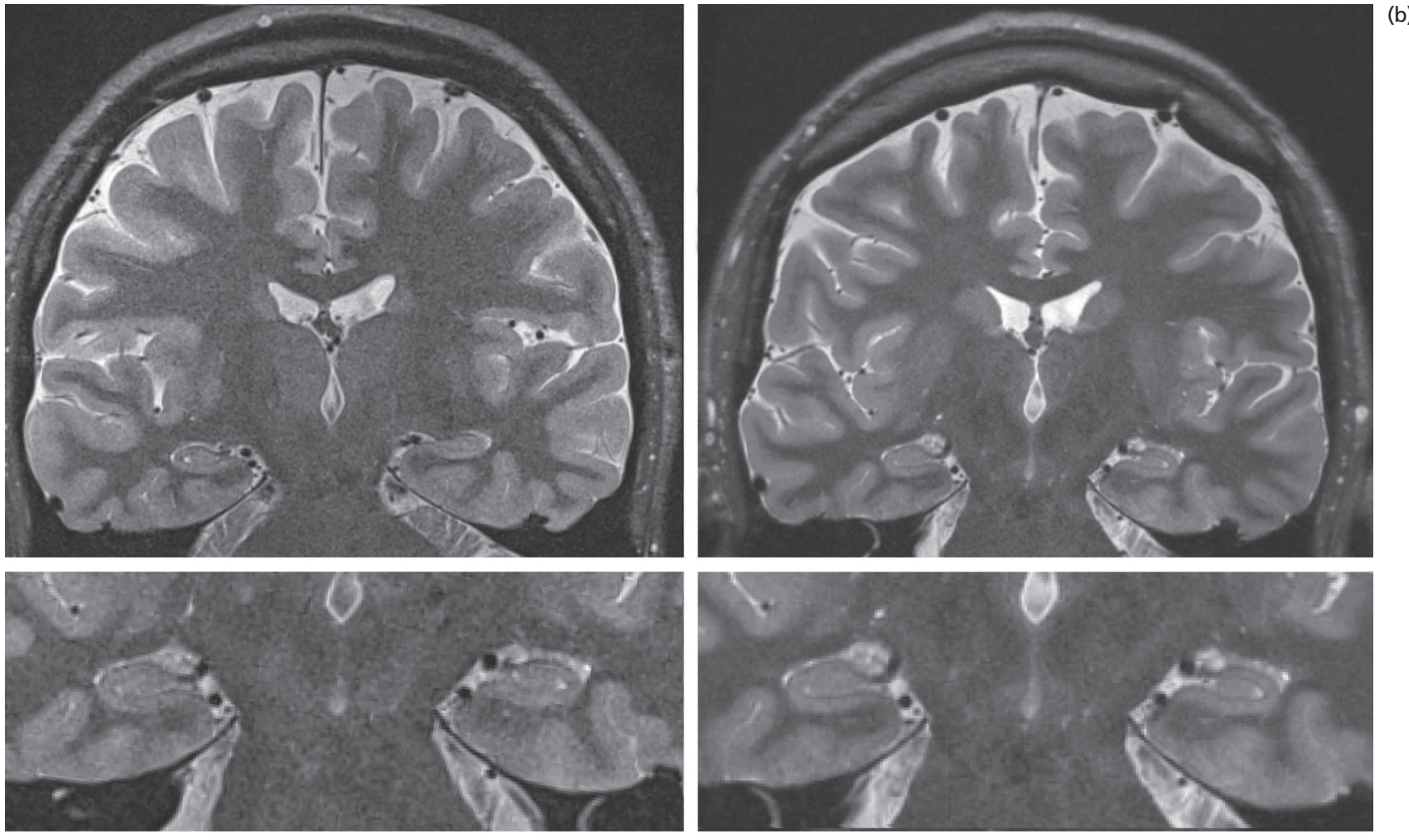

Fig. 64.1 Comparison of resolution and contrast between 1.5-tesla MRI (a) and 3-tesla MRI (b) in a healthy adult. Both images are acquired with a T2-weighted sequence with an additional inversion pulse prior to image acquisition [short time inversion recovery (STIR)] with 40 2-mm slices, no gap. (a) Siemens 1.5-T Avanto: TR 5600 ms, TE 17.0 ms, TI 100 ms, acquisition time 7.29 min. (b) Siemens 3.0-T Trio: TR 5600 ms, TE 18.0 ms, TI 100 ms, acquisition time 9.30 min. Note the better signal–noise ratio on the 3-T MRI. The hippocampal structure can be better identified on the 3-T MRI.

Table 64.2 Recommendation for a staged application of CCT, 1.5-T MRI and 3-T MRI. In rare cases CCT may be helpful in addition to MRI for the diagnosis of lesions that can present with intralesional calcification (dysembryoplastic neuroepithelial tumours (DNETs), gangliogliomas, tubers of tuberous sclerosis).

Clinical setting	Recommendation
First seizure (acute setting)	CCT
First seizure (subacute setting), or beginning epilepsy, or long-lasting epilepsy but lack of sufficient imaging, or presurgical evaluation and MRI finding consistent with epilepsy syndrome	1.5-T MRI, if available 3-T MRI
If 1.5-T MRI is inconclusive/non-lesional and first two AEDs do not lead to seizure control, or if 1.5-T MRI is inconclusive/non-lesional and the patient undergoes a presurgical evaluation	3-T MRI

Epilepsy-specific MRI protocols

It is not just the field strength of MRI scanners that determines the yield of diagnostic MRI. Two other important aspects are the optimal choice of MRI sequences and the optimal orientation/angulation of images. The latter is essentially based on the assumption of whether a temporal or extratemporal focus is expected. With this *a priori* information the referring epileptologist can increase the sensitivity of the MRI examination.

Recommendations regarding sequences depend on the prevalence of lesions in epilepsy patients and their MRI properties. The most common sequences are: *T1 (longitudinal relaxation)-weighted imaging* [very short echo time (TE) and intermediate repetition time (TR), good contrast and anatomical resolution, poor lesion detection power]; *T2 (transversal relaxation)-weighted imaging* (intermediate TE and very long TR, relatively good resolution, sensitive to water content and

Table 64.3 Overview of preferred MRI sequences and expected signal alterations for the most common lesions found in epilepsy patients who are referred for persurgical evaluation (1.5-T; modified from ref. 7).

Aetiology	Preferred sequences	Signal changes	Other features	Example (Fig.)
Mesial temporal sclerosis (MTS/AHS)	T2/STIR, FLAIR	Hippocampal T2/STIR ↑, FLAIR ↑	Hippocampal atrophy, loss of internal structure	3, 5
FCD IIB	FLAIR	Subcortical>cortical FLAIR↑	Blurred grey–white matter junction, funnel towards ventricle, thickened cortex	2b, 4, 9, 13
FCD IIA	FLAIR	FLAIR↑ (↑)	Blurred grey–white matter junction, (thickened cortex)	–
Periventricular nodular heterotopia (PNH)	T2/STIR, T1-IR, 3D-T1	Cortex isointense	Often located at the lateral ventricles, often in clusters Overlying cortex mostly MRI normal	2a, 11c, 12d
Polymicrogyria (PMG), schizencephaly (SE)	T2/STIR, T1-IR, 3D-T1	Cortex isointense	PMG: multiple small gyri, often perisylvic; SE: complete or incomplete hemispheric cleft, often lined with PMG	11a, 12a and b
Subcortical band heterotopia (SBH; double cortex)	Sagittal or 3D-T1	Nearly cortex isointense subcortical band	SBH can be discontinuous and asymmetric, even very subtle	12c
Ganglioglioma	T2/STIR + FLAIR	Cysts in T2/STIR ↑, solid component in FLAIR ↑	Often cystic component, CM enhancement <50%	2c, 8b
DNT/DNET	T2/STIR + FLAIR	Cysts in T2/STIR ↑	Often multicystic or large, septated cyst, predominantly intracortical	8a
Cavernoma	T2*, T2, T1 + CM	Signal extinction (haemosiderin ring), CM+	Occasionally multifocal	8c
Arteriovenous malformations	T2* T2, T1 + CM	CM+ convolute of vessels, signal extension in T2*	Notch-like configuration	–
Traumatic brain injury	FLAIR, T2/STIR, T2*	Gliosis: FLAIR↑ STIR↑, hemosiderin T2* ↓	Often multiple, contrecoup	2a, 10a
Tuberous sclerosis	FLAIR, T2/STIR	Tubers, SEGA: FLAIR ↑ T2/STIR ↑, calcifications: FLAIR and T2/STIR ↓	Cortical tubers, calcifications, CM enhancement possible, SEGA	11b
Rasmussen's encephalitis	FLAIR, T2	FLAIR↑ STIR↑	Initial focal swelling, progressive unilateral atrophy	10c
Sturge–Weber	T1-CM, T2/STIR, T2*	T2/STIR↑ ↔, T2*↓	Calcifications, atrophy, angioma, epicortical CM enhancement	–
Hypothalamic hamartoma	Cor T1, T2/STIR	T1↑, T2/STIR↓	Gelastic seizures	11d
Pachygyria, lissencephaly	All, 3D surface-rendering	–	Thickened cerebral cortex with few and large gyri	–

Note: This list is intended to provide an overview for epileptologists. It does not replace the expertise of a trained neuroradiologist who is experienced in the interpretation of MR scans of epilepsy patients.

AHS, ammons horn sclerosis; CM, contrast medium; DNT/DNET, dysembryoplastic neuroepithelial tumour; FCD, focal cortical dysplasia; MTS, mesial temporal sclerosis; SEGA, subependymal giant cell astrocytoma; T1,T2, T2*, FLAIR, STIR, T1-IR: MRI sequences, *see text*.

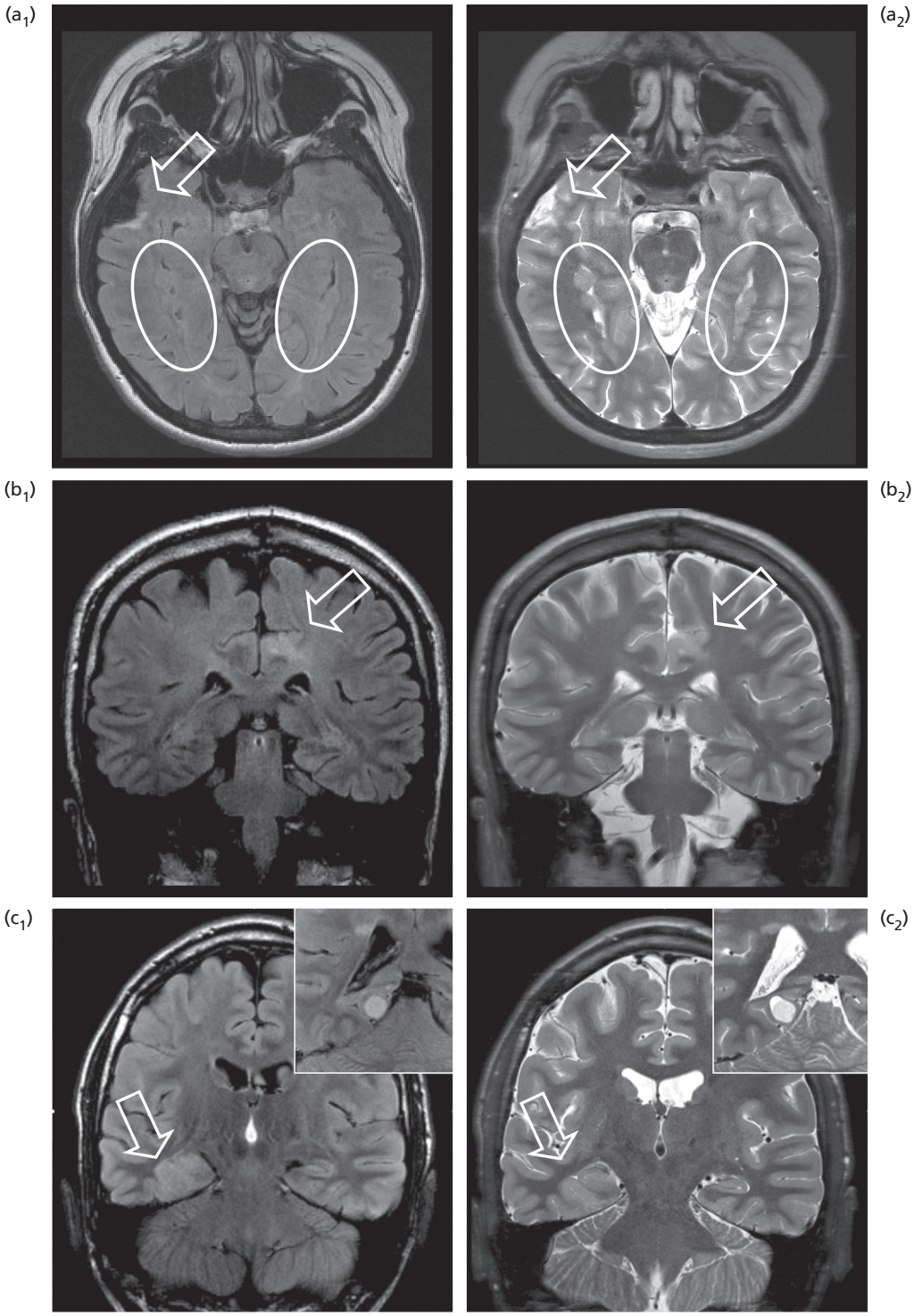

Fig. 64.2 Not all lesion types are equally easy to see in all sequences. (a) The bilateral periventricular nodular heterotopia is more likely to be overseen on the FLAIR (a_1) than on the STIR (a_2) image. In contrast, the concomitant right temporolateral post-traumatic defect (arrow) is possibly easier to recognize in FLAIR. (b) A focal cortical dysplasia (type IIB, arrow) in the left dorsal cingulate gyrus is easier to recognize in FLAIR (b_1) than in STIR (b_2). (c) A ganglioglioma (WHO grade I) presenting with a cystic (inset) and a solid component. The solid component of the lesion extends to the anteromesial temporal lobe and can be seen more easily in FLAIR (c_1) than in STIR (c_2). These differences may determine whether or not a lesion or its extent is correctly detected, particularly for a radiologist with limited experience with epileptogenic lesions.

therefore good lesion detection power); *FLAIR* (modification of T2 with suppression of free water by an inversion pulse for better lesion detection); and *T1-inversion recovery* (same applied to T1, excellent grey–white matter contrast). T2 signal quality can be enhanced by an additional inversion pulse before actual image acquisition (TI ~100 ms), which suppresses fat signal [short time inversion recovery (STIR)]. For the technical details of different sequences as well as detailed lesion properties, refer to MRI textbooks. A practicable overview of characteristic signal alterations associated with common epileptogenic lesions is provided in Table 64.3. Examples underlining the necessity to apply several MRI sequences to patients are provided in Fig. 64.2.

Each MRI examination should comprise at least three different sequences and three different orientations (coronal, transversal and sagittal). To avoid missing small lesions and to avoid partial volume effects, slice thickness should not exceed 5 mm/no gap.

In regions of interest (at the request of the epileptologist) even thinner slices can be helpful. The T1-weighted images are often acquired as sagittal *m*agnetization *p*repared *ra*pid *g*radient *e*cho (MPRAGE) with isotropic voxels (i.e. $1 \times 1 \times 1$ mm/no gap). These three-dimensional datasets can be reoriented and resliced for the precise anatomical localization of lesions seen in other sequences, but can also be used for postprocessing or fusing multiple imaging modalities. Recommendations for epilepsy-specific, basic MRI imaging are given in Table 64.4. The duration of data acquisition for the basic protocols is about 35–40 min. Going below this basic standard in order to shorten the examination time increases the danger of missing therapy-relevant lesions.

Using the temporal instead of the anterior commissure–posterior commissure (AC–PC) angulation in patients with temporal lobe epilepsy (TLE) might make mesiotemporal sclerosis easier to identify. On the other hand, temporal angulation renders the localization of lesions in the central region and in the frontobasal/orbital cortex more difficult. This fact emphasizes the importance of obtaining a detailed patient history (particularly seizure semiology) before performing an MRI. Figure 64.3 illustrates the principle of temporal and AC–PC angulation.

If patients are considered for presurgical evaluation then they may require MRI examinations that exceed the minimum standard. Additional examinations may comprise more sequences or orientations (e.g. sagittal FLAIR), other presentation formats such as curved surface projection ('pancake' – Fig. 64.4) [11], or additional MRI techniques such as fMRI or diffusion tensor imaging (DTI) (discussed later in this chapter).

Before surgery, patients should have had the best possible imaging. The rationale behind this is that detecting and correctly estimating the extent of epileptogenic lesions are not the only factors that determine whether or not a patient is a good surgical candidate. High-resolution imaging can also reveal secondary lesions that might not have been identified with less sophisticated examinations. In a recently described illustrative case a patient suspected of having cryptogenic left temporal lobe epilepsy was found to be suffering from bilateral subcortical band heterotopia. This was only recognized after MRI postprocessing but still prior to invasive recordings or surgery [12]. With less imaging effort this patient might have been exposed to unnecessary risk.

Technical progress is being made in different fields at present. It remains to be seen whether or not new MRI sequences such as double inversion recovery [13] or PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) [14] or the improvement of head coil technology [15] or field strengths that are higher than 3 T will further improve presurgical MRI.

Table 64.4 Recommendations for basic and special MRI protocols in patients with epilepsy.

Temporal lobe epilepsy: basic protocol	
Hippocampal oriented T2-weighted (coronal + axial)	
Hippocampal-oriented fluid attenuation inversion recovery (FLAIR) (coronal + axial)	
Isotropic T1-weighted three-dimensional sequence (MPRAGE)	
(Gadolinium contrast enhanced T1-weighted image if non-contrast enhanced image is inconclusive)	
T2*-weighted sequence	
Extratemporal lobe epilepsy: basic protocol	
AC–PC oriented T2-weighted (coronal + axial)	
AC–PC oriented FLAIR (coronal + axial)	
Isotropic T1-weighted three-dimensional sequence (MPRAGE)	
(Gadolinium contrast-enhanced T1-weighted image if non-contrast enhanced image is inconclusive)	
T2*-weighted sequence	
Special protocols	*Rationale*
T2-relaxometry	Hippocampal signal abnormalities
MR-spectroscopy	Detection of metabolic abnormalities
Diffusion tensor imaging (DTI)	Investigation of fibre tracts
Funtional MRI	Investigation of eloquent cortical areas
Three-dimensional sequences	Automated voxel-based analyses
MR-angiography	Investigation of brain vascularization

Time for performing the basic protocols is about 35–40 min. Instead of T2 we perform T2-STIR sequences (see text).

Examples of common epileptogenic lesions

In the following section we present typical features of pathologies that are commonly associated with epilepsy. To allow for a systematic approach of the heterogeneous aetiologies, we followed the principle of easy (A), moderately difficult (B), very difficult (C), palliative (D) and non-surgical candidates (E).

Class A: easy candidates

For successful epilepsy surgery, the classical 'easy' patient is the one who presents with a clear history of mesial temporal lobe epilepsy (MTLE) and shows unilateral mesial temporal sclerosis [MTS, also referred to as Ammon's horn sclerosis (AHS)]. In the past, seizure freedom rates used to be around 65% (meta-analysis of Téllez-Zenteno and colleagues [16] evaluating studies published between 1990 and 2003), but with modern imaging and elaborate presurgical work-up in selected patients seizure freedom rates can exceed 80% [17]. The MRI features of MTS are signal increases in FLAIR and T2/STIR and atrophy of the hippocampus. Depending on the MRI quality, another frequent feature of MTS is a loss of internal hippocampal structure [18]. A typical example of left-sided AHS is shown in Fig. 64.5.

However, diagnosing of MTS is not always easy. On the one hand, the visual identification of MTS is mostly based on the comparison of the left and right hippocampi. If both are relatively small and show some signal intensity, it can be difficult to discriminate bilateral MTS from bilaterally small, but still normal, hippocampi. Here, hippocampal volumetry and relaxometry can be helpful (discussed later in this chapter).

On the other hand, if only single MRI features of MTS are present, other diagnoses must also be taken into account. T2/FLAIR signal increases in combination with normally large or swollen hippocampi or amygdalae, for example can occur in acute limbic encephalitis [19], and transiently after a series of seizures [20]. Figure 64.6 shows an example of the course of hippocampal volume and signal changes through the different stages of an acute limbic disorder [suggestive of voltage-gated potassium channel

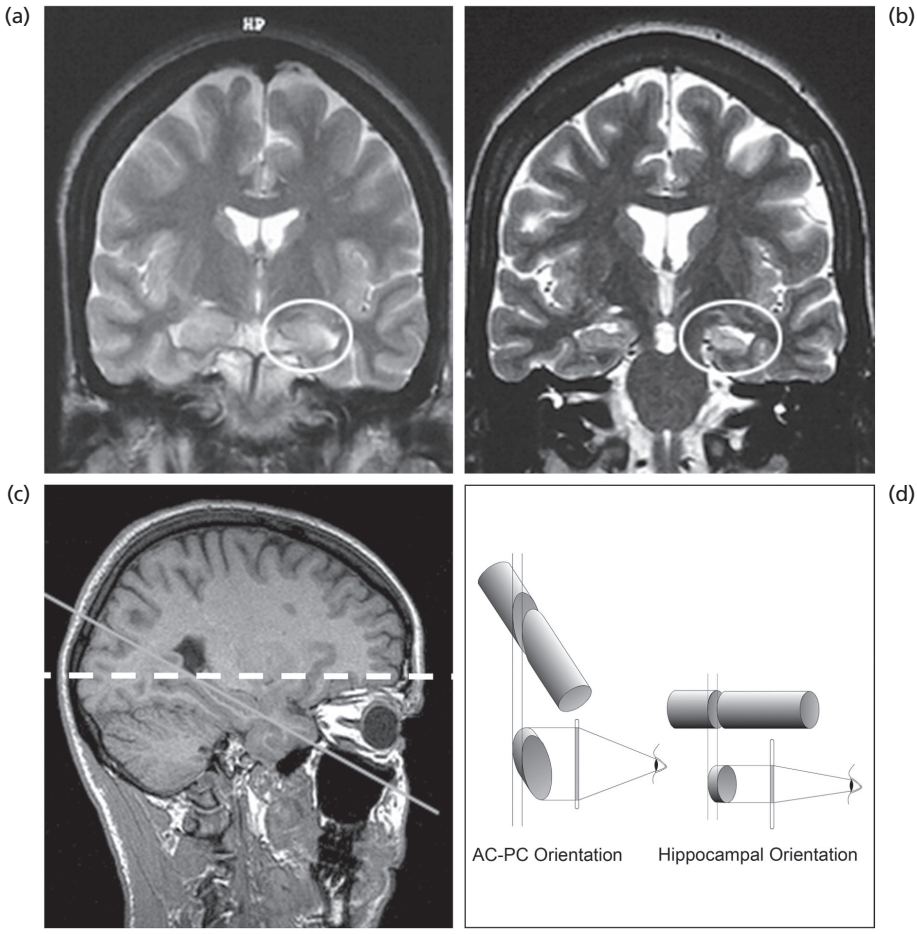

Fig. 64.3 Importance of the correct angulation of the MR scan in a patient with MTLE and a left mesiotemporal sclerosis. In (a), AC–PC oriented, the diagnosis of MTS is far more difficult to discern than in (b) (same patient, MRI orientated along the hippocampal axis). (c) and (d) illustrate the principles of AC–PC and hippocampal orientation. (a) and (b) modified from ref. 7.

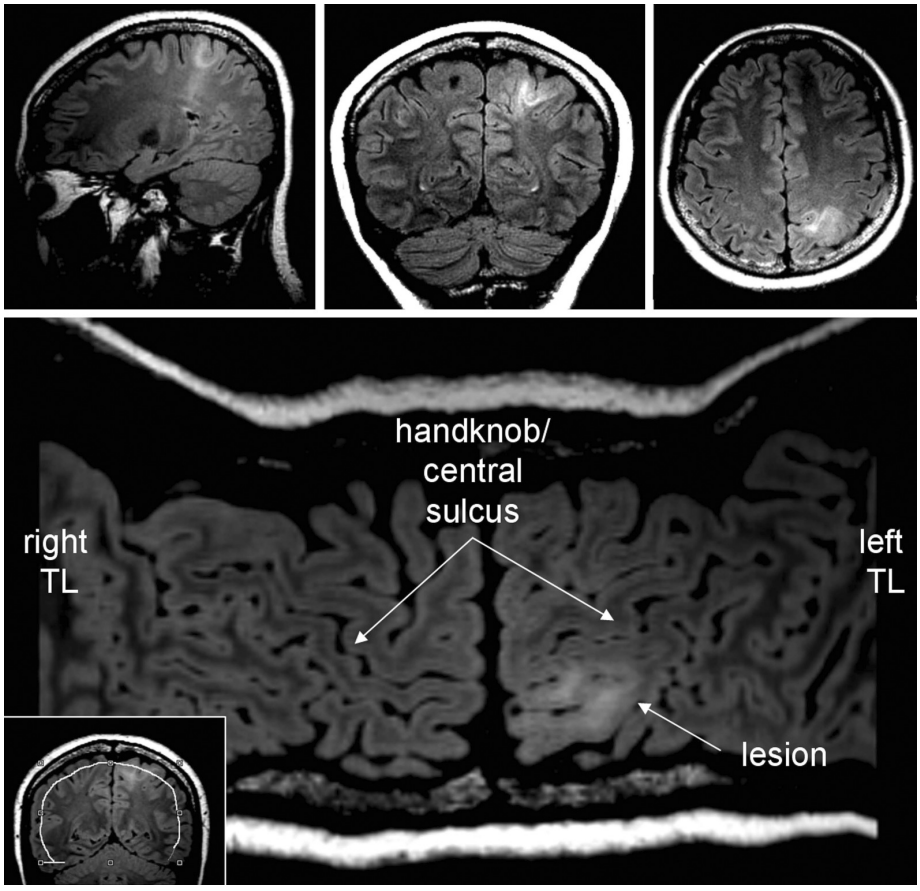

Fig. 64.4 A patient with focal cortical dysplasia in the left post-central area. The lesion is easy to recognize in the axial, sagittal and coronal planes, but its exact localization in relation to the precentral gyrus is better illustrated in the curved surface projection ('pancake').

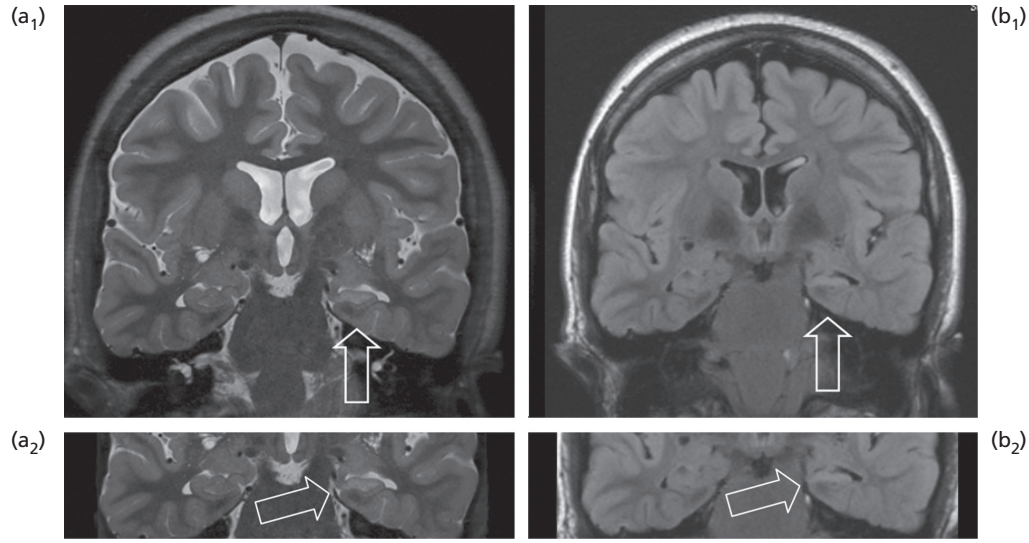

Fig. 64.5 A typical example of unilateral left MTS, showing a loss of hippocampal volume, a signal increase and a loss of internal anatomical structure on the pathological side. (a_1) and (a_2), STIR; (b_1) and (b_2), FLAIR.

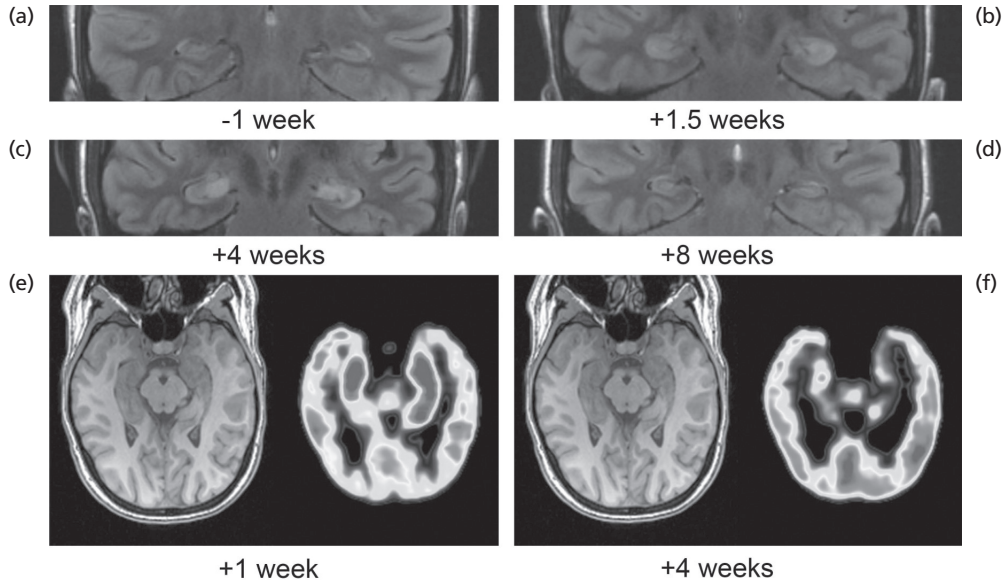

Fig. 64.6 Images of a 23-year-old woman with suspected acute limbic encephalitis. After experiencing two generalized tonic–clonic first-time seizures, she was referred to our department. Her first MRI was non-lesional. She did not experience any further seizures and had no neuropsychological deficit until 2 weeks later when she developed a complex partial status epilepticus and an amnestic syndrome. Under anticonvulsive and anti-inflammatory (intravenous immunoglobulins, cortisone pulses) therapy, seizures stopped within days and an improvement in amnestic function was documented over the following months. (a) to (d) Time-course of signal intensity and hippocampal volume in both hippocampi (all images 3T Siemens, FLAIR). (e) and (f) Concomitant to MRI changes, we observed a marked bitemporomesial hypermetabolism in FDG-PET at the early stage, and a left pronounced hypometabolism 4 weeks after initiation of therapy (both PET are coregistered to the 3D-T1 MRI at –1 week). The time points refer to the beginning of the complex partial status.

(VGKC)-negative limbic encephalitis]. This course illustrates that for those patients with recent seizure manifestation, singular MRIs might be misleading. In case of doubt, we recommend performing a second MRI some weeks to months after the initial MRI. Patients with acute limbic encephalitis are usually not considered surgical candidates.

Features of still uncertain relevance are a blurring of the grey–white matter junction and a signal increase in the white matter in the anterior part of the affected temporal lobe. They are predominantly found in patients with MTS and seizure onset before the second year of life, and are most likely the result of impaired myelinization [21]. However, whether the presence of this feature indicates a wider epileptogenic zone which makes temporal pole resection in addition to amygdala-hippocampectomy necessary for seizure freedom is not yet clear. An example of disturbed grey–white matter demarcation is shown in Fig. 64.7.

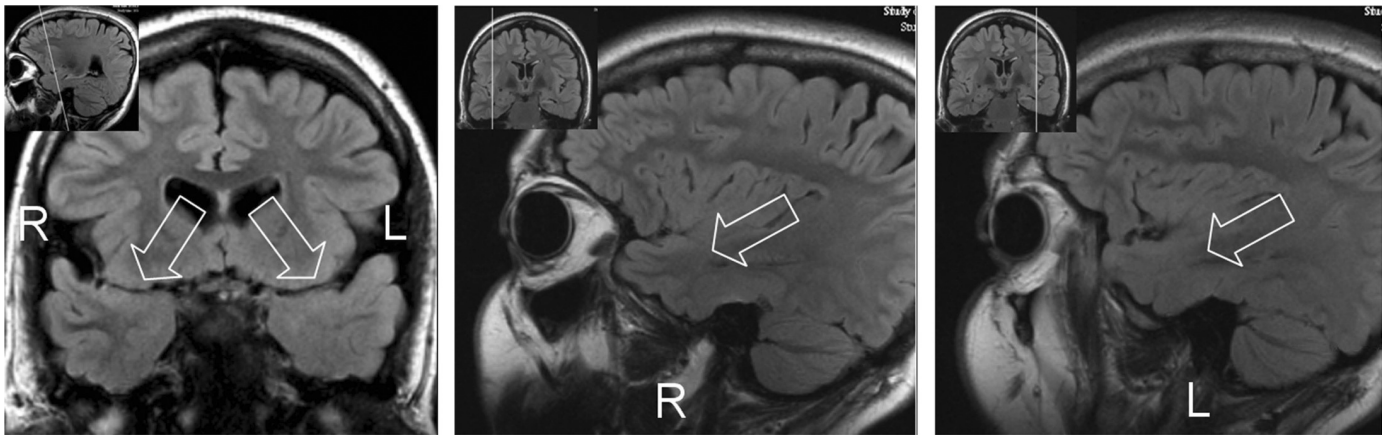

Fig. 64.7 Typical example of a grey–white matter junction blurring and increased temporopolar white matter signal in the left temporal lobe of a patient with left MTS and seizure onset in the first year of life (same patient as in Fig. 64.5).

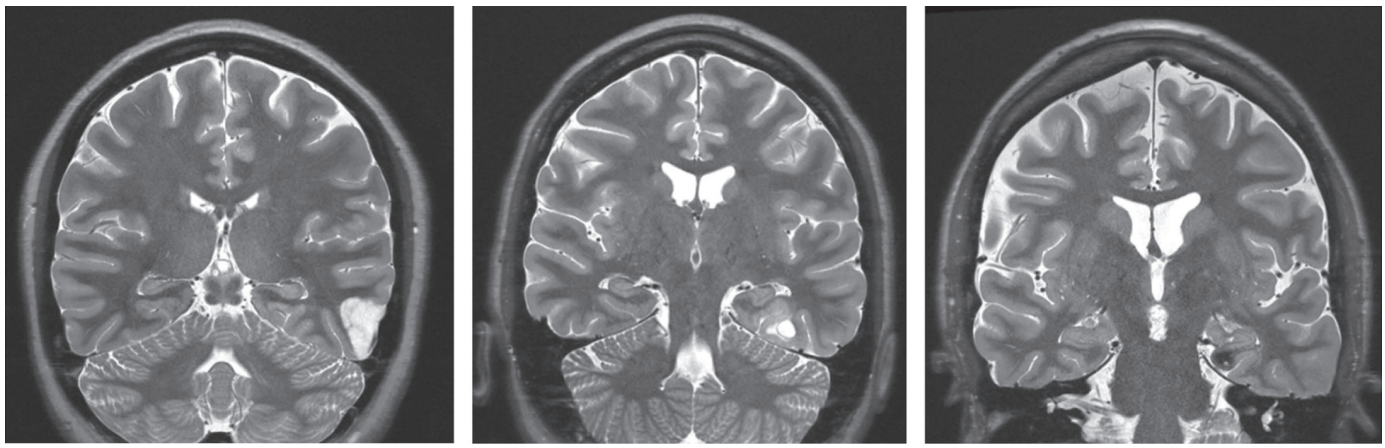

Fig. 64.8 Three patients with highly epileptogenic but easily accessible lesions. (a) Dysembryoplastic neuroepithelial tumour (DNET) WHO grade I. (b) Ganglioglioma WHO grade I. (c) Venous cavernoma. All lesions are known to be highly epileptogenic. If the seizure semiology and interictal/ictal EEG fit with the location of the lesion then these patients are excellent surgical candidates (through extended lesionectomy).

Patients who show easily accessible singular lesions that are known to be epileptogenic and whose localization is concordant with the clinical and EEG presentation of the seizures are even better surgical candidates than those with MTLE. Typical examples include patients with dysembryoplastic neuroepithelial tumours (DNT/DNETs) and glioneuronal tumours (gangliogliomas, gangliocytoma) [22]. Patients with single venous cavernomas also have a very high chance of achieving seizure freedom if a complete resection is possible [23]. However, as multiple cavernomatosis exists and the resection of only one of several cavernomas is not as likely to result in seizure freedom, sequences with high sensitivity for haemosiderin-induced susceptibility artefacts should be applied [T2* of fast field echo (FFE)] [24]. Figure 64.8 shows examples of lesions in easy-to-operate candidates (class A). Recognizing the named entities is not only important from the epilepsy surgery point of view. Some of these lesions can have large extensions and look bizarre; they may also take up contrast medium and therefore be misdiagnosed as high-grade tumours and wrongly treated as such. However, most of these tumours have no growth potential [22]. Extended lesionectomy usually leads to favourable seizure outcome.

Another type of lesion which can be attributed to class A epilepsy surgery candidates is circumscribed focal cortical dysplasia type IIB (FCD IIB), according to Palmini and Lüders [25]. Although not completely overlapping, in other nomenclatures these lesions are referred to as Taylor-type dysplasia [26] or cortical dysplasia with balloon cells [27]. This entity is highly epileptogenic. When FCD IIB is located remotely from eloquent cortex and is easy to delineate on MRI (showing a markedly hyperintense, funnel-shaped area in the white matter, which may extent towards the ventricle [28]), very high surgical success rates can be achieved through MRI-based extended lesionectomy [29]. If, however, dysplasia with balloon cells is rather diffuse [such in the case of transmantle dysplasia or (partial) hemimegalencephaly] or

lesions are located close to eloquent cortex then patients have to be placed in a category other than the easy-to-operate candidates. (For examples of focal cortical dysplasia, see Figs 64.2, 64.4, 64.9 and 64.13.)

Class B: moderately difficult candidates

Patients attributed to class B may have lesions that are identical to those of class A patients. However, their localization requires a more complicated, potentially risky, presurgical evaluation (i.e. invasive recording or mapping with implanted subdural or depth electrodes) or they run a higher risk of postoperative functional deficits.

This category also comprises patients with a slightly to moderately reduced chance of postoperative seizure freedom. As previously mentioned, patients with malformation of cortical development (MCD) other than the circumscribed FCD IIB belong to this group (Fig. 64.9c and d). It will be an issue for clinical research to determine if 3-T MRI combined with improved sequences and postprocessing allows one to better identify the extent of cortical malformations and thus result in the improved categorization of good and bad surgical candidates.

Class B surgery candidates may also be those with post-traumatic defects. Although some small studies report favourable outcome after complete resection of trauma-induced encephalomalacia [30], post-traumatic seizures are reported to occur in particular in patients with multiple post-traumatic defects [31]. Resection of multiple, bihemispheric defects, however, is mostly impossible. Another problem are patients with primary epileptogenic lesions with secondarily acquired traumatic brain injury. It is likely, but not yet proven, that patients with secondary brain injury have a lower chance of achieving seizure freedom after resection of the primary epileptogenic lesion (but sparing the

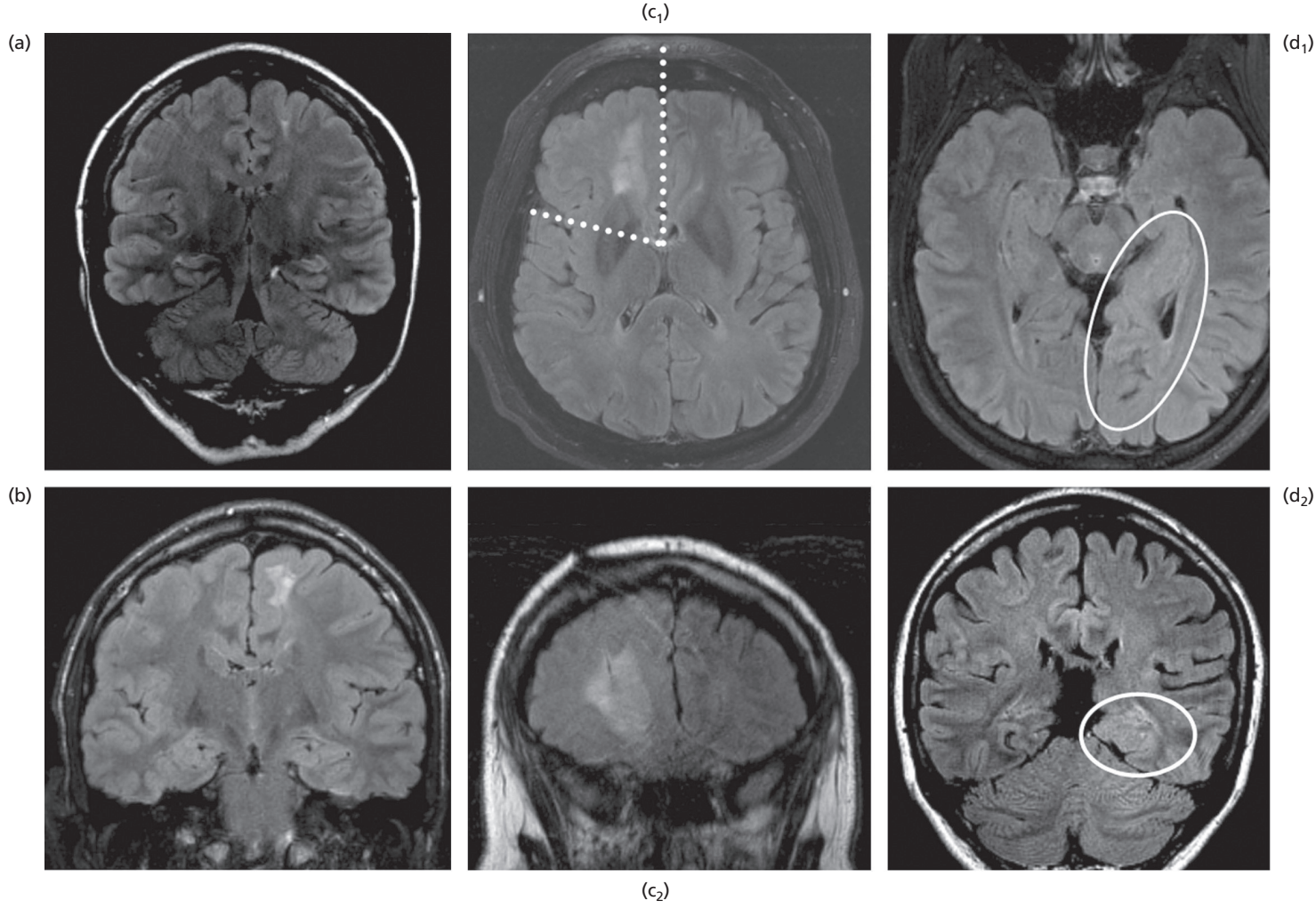

Fig. 64.9 Four patients with different malformations of cortical development. (a) A circumscribed FCD IIB (according to Palmini and Lüders [25]) left frontodorsal. (b) Larger FCD IIB in the left supplementary motor area (SMA). (c_1) and (c_2). Large balloon cell containing malformation of the entire right frontal lobe (see dotted line). Better than FCD IIB, this lesion may be categorized as transmantle dysplasia or partial hemimegalencephaly (in the classification of Barkovic *et al.* [27]). (d) Diffuse malformation of the left temporomesial to occipital structures. Histology showed ectopic neurones in the white matter, no balloon cells and no dysmorphic neurones. Therefore, despite clear pathology in MRI, this pathology cannot be classified according to present classifications. Patients in (a) and (b) are easy surgery candidates (class A patients}, whereas the patients in (c) and (d) belong to class B or C, depending on whether or not the limits of dysplasia/the necessary extent of resection can be detected by MRI or invasive recordings.

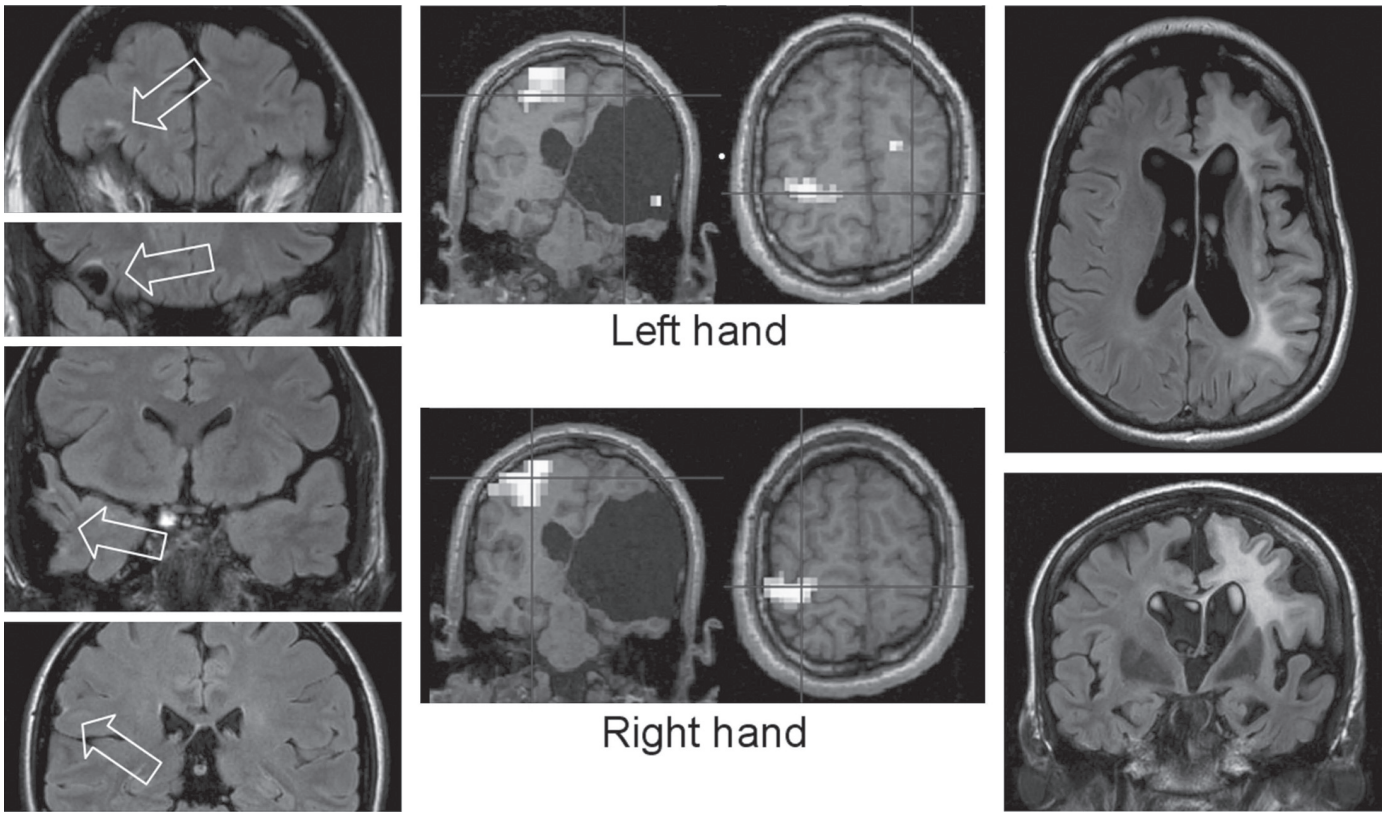

Fig. 64.10 (a) A patient with multiple right hemispheric post-traumatic substance defects (see arrows). Note that in FLAIR even subtle defects can be detected. (b) A patient with porencephaly of the left hemisphere due to perinatal media infarction. There was some preserved motor function of the right hand, but the fMRI indicates ipsilateral representation of the right hand motor function. After a functional hemispherotomy, the patient was seizure free (4.5 years off medication) and there was no deterioration of motor function. (c) Rasmussen's encephalitis of the left hemisphere.

post-traumatic lesion) than those without secondary brain damage. However, with regard to presurgical MRI it is essential to search for even subtle post-traumatic defects if the patient reports a positive trauma history. Examples of post-traumatic lesions in MRI are shown in Figs 64.2 and 64.10.

Patients with porencephaly due to perinatal media infarction can also be classified as class B surgical candidates. Their seizure freedom rate is high [32,33], but the presurgical evaluation is usually more complicated than that of class A patients. Although presurgical hemiparesis is common, usually some motor function in the paretic side is preserved. Patients often undergo fMRI (see Fig. 64.10) or Wada test before surgery. Because of its ipsilateral representation, motor function is usually preserved after hemispherectomy/functional hemispherotomy.

A matter of controversy is when to operate on a patient with Rasmussen's encephalitis. The decision will be influenced by the dominance of the hemisphere and made only after individual risk–benefit estimation [34]. However, because hemispherectomy is a real therapeutic option for many patients, a first presurgical evaluation should not take place too late in the course of the disease. Therefore, we propose to classify these patients as class B surgical candidates.

Class C: very difficult surgical candidates

Patients who do not show lesions on MRI (cryptogenic patients) are bad surgical candidates because they require comprehensive, often invasive, presurgical work-up and their chance of postoperative seizure freedom is relatively small [35]. Much effort should be undertaken to detect existing lesions (by 3-T MRI, post processing) because this can still make patients class A or B candidates with a better chance of seizure freedom. If the best available MRI is non-lesional, it can be reasonable to postpone surgery and speculate on improving future imaging rather than performing an unsuccessful surgery. At this point, we must allude to the fact that the implantation of a vagal nerve stimulator (VNS) should be considered critically in non-lesional patients. With a VNS, access to an MRI higher than 1.5 T is restricted and thus VNS can hinder the imaging process and adversely affect the patient's realistic chance of curative surgery.

Other class C surgical candidates show lesions that usually entrain poor seizure outcome. Depending on the individual risk–benefit ratio, surgery should be performed only in desperate seizure situations and after proof of pharmacoresistance to multiple drugs. One explanation for this is that the epileptogenic area may exceed the MRI-detectable lesion or that these lesions are multifocal or bilaterally distributed. For example, this is true for

polymicrogyria (PMG) and the polymicrogyria–schizencephaly complex. However, optimized imaging may help in detecting the extent of the malformation, and complete resection may result in favourable outcomes in patients with unilateral PMG [36]. Although 3-T MRI shows polymicrogyria to a much better extent than 1.5 T, it is still unknown if this has any impact on the surgical outcome.

Patients with monofocal nodular heterotopia must also be considered very difficult surgical candidates, as the extent of the epileptogenic zone will exceed the nodule (including parts of the overlying cortex [37,38]) and the identification of the epileptogenic zone requires invasive recordings. After careful selection, however, patients with unilateral periventricular nodular heterotopia (PNH) can profit from surgery [38]. If multiple heterotopic nodules are detected then postoperative seizure freedom is unrealistic. Therefore, high-quality MRI (in particular with T1- or IR-sequences) is essential to identify non-operable patients (class E).

Despite promising results in selected patients [39], most patients with multiple tubers in tuberous sclerosis must also be classified as very difficult surgical candidates. For these patients, the staged epilepsy surgery approach has been proposed [40,41]. Before this risky, multistep surgery is considered, the patient should be proven pharmacoresistant for multiple medications.

Patients with hypothalamic hamartomas are also class C patients (see ref. 42 for radiological features of hypothalamic hamartomas). The chance of seizure freedom after surgery is not very high and surgery of hypothalamic hamartomas is not free from complications. It remains to be seen whether or not radiosurgery will finally offer a better risk–benefit ratio than resective surgery [43,44]. Figure 64.11 shows some examples of patients considered class C or D.

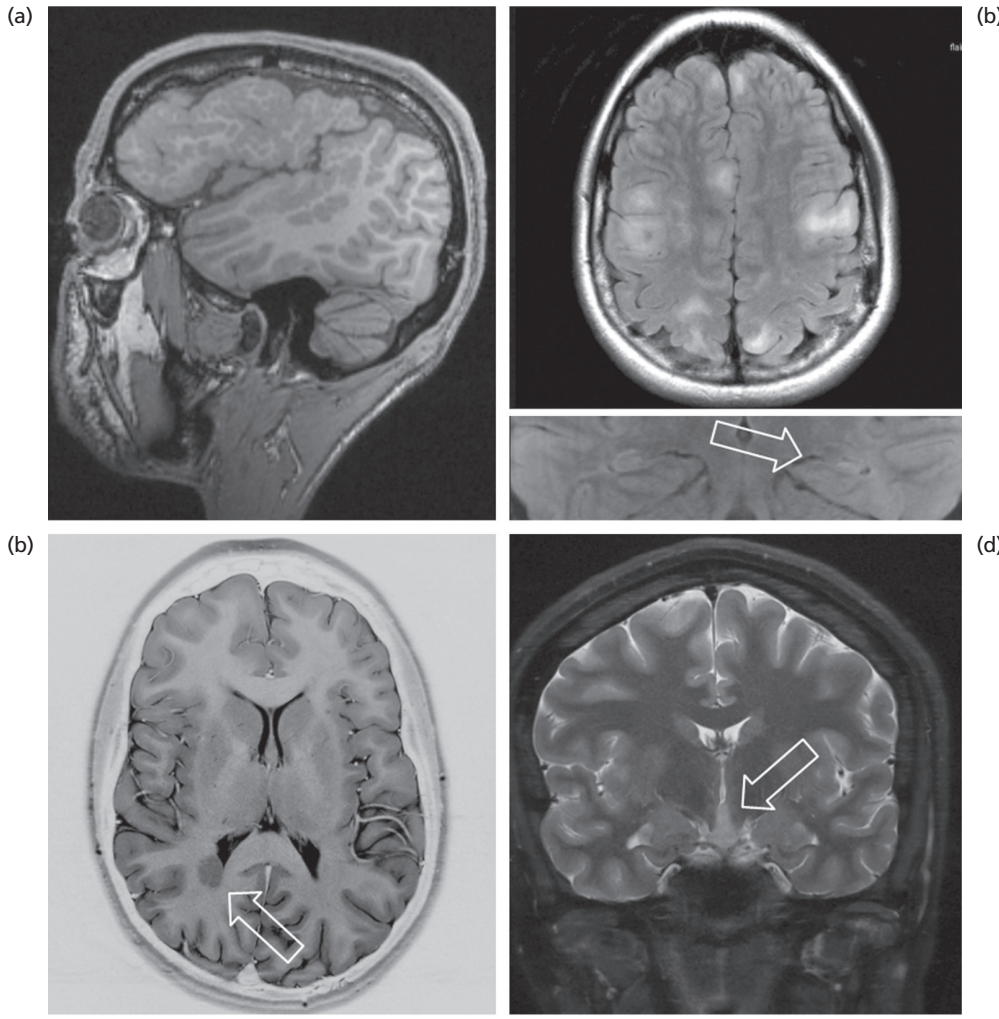

Fig. 64.11 Very difficult or palliative surgical candidates. (a) A patient with extended unilateral right polymicrogyria (3D-T1). Because of multiple seizures per week, often with severe injuries, and pharmacoresistance to virtually all AEDs the patient qualifies for surgery. However, because of bad prospects for seizure freedom and inevitable postoperative neurological deficits he is considered a class C to D candidate. If polymicrogyria is detected contralaterally as well then this patient will be classified as a non-surgical candidate (class E). (b) A patient with multiple tubers in tuberous sclerosis and left MTS. Her seizures have clear left temporomesial semiology and the EEG shows left temporal seizure onset. With a clearly reduced chance of seizure freedom, this patient can be offered left temporal lobe surgery (as a candidate for palliative surgery – class D). (c) A patient with monofocal periventricular heterotopia. Epileptogenicity of the overlying cortex is possible and determining the necessary extent of surgery is complicated; as such this patient would be assigned to class C or D. (d) A typical example of a hypothalamic hamartoma (class C).

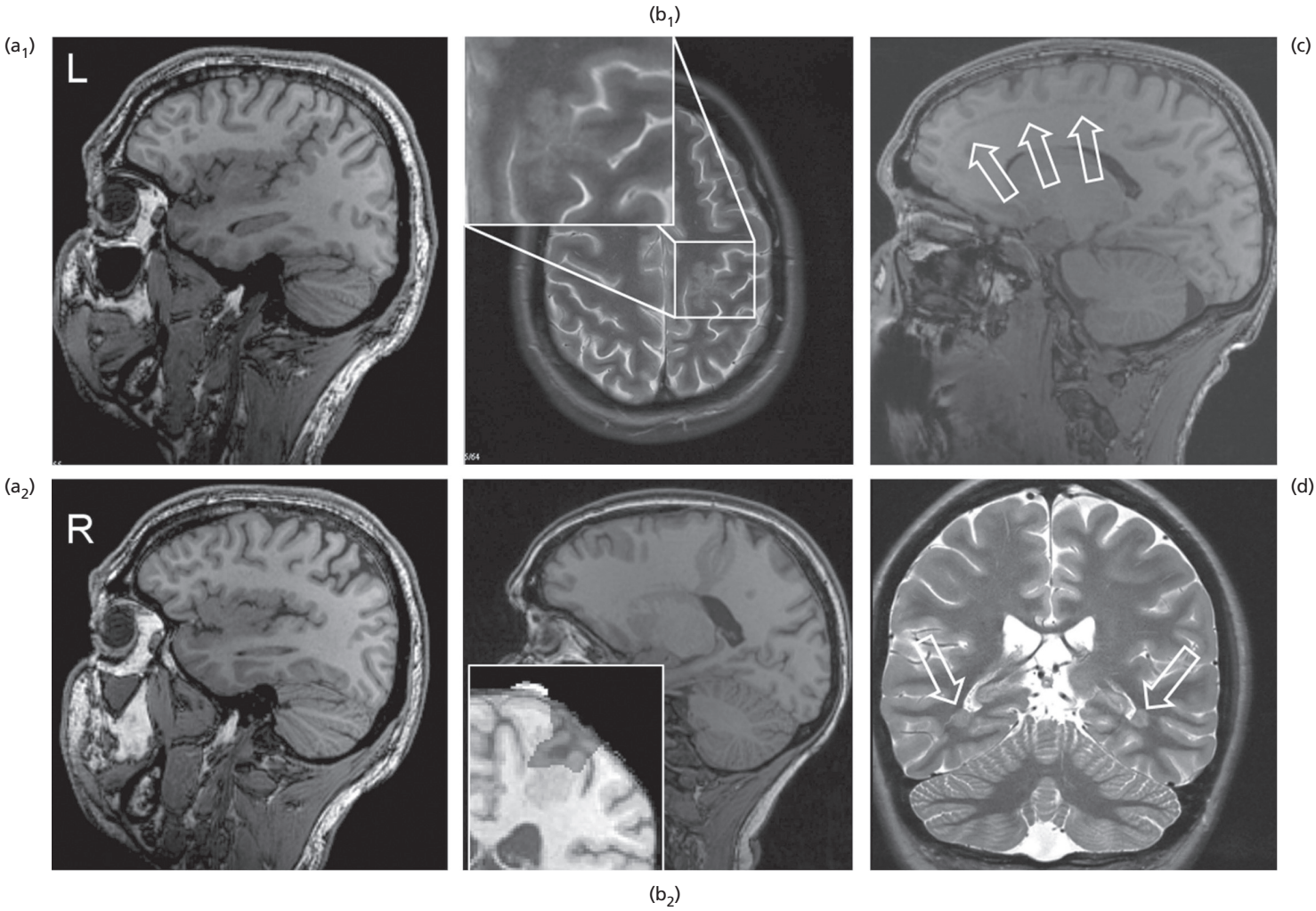

Fig. 64.12 Non-surgical candidates. (a_1) and (a_2) A patient with left and right hemispheric perisylvian PMG. (b_1) and (b_2) PMG schizencephaly-type lesion in the central region. fMRI (inset) indicates the overlap of motoric hand representation and malformation. (c) A patient with prominent subcortical band heterotopia. (d) A patient with bilateral periventricular nodular heterotopia.

Class D: palliative surgery candidates

Palliative surgery is undertaken when epilepsy surgery cannot realistically bring about seizure freedom but may result in relief from particularly disabling seizure types. Typical examples are patients who undergo a corpus callosotomy for relief from tonic or atonic drop attacks. Also patients who undergo resection of only one out of several proven seizure foci can be considered class D. These candidates can have all types of lesions or be cryptogenic. One exemplary case is shown in Fig. 64.11b.

Class E: non-surgical candidates

Reasons for not performing epilepsy surgery on a patient include no chance of achieving seizure freedom or the likelihood of unacceptable neurological deficits. Among the first of the conditions that fall into this category are bilateral migration disorders such as bilateral periventricular nodular heterotopia [37,45], bilateral polymicrogyria or double cortex syndrome (subcortical band heterotopia [46]). Double cortex syndrome can be very prominent and is detectable on all sequences. However, there are very subtle forms that can be recognized only on high-resolution sagittal or three-dimensional T1 images or only through postprocessing [12]. Also, complex malformations such as pachygyria and lissencephaly are not curable by epilepsy surgery, although their detection is usually not difficult using MRI.

Lesions overlapping the eloquent cortex also preclude surgical therapy. They are not restricted to certain aetiologies. Figure 64.12 shows examples of class E patients.

MRI postprocessing

Identifying malformations of cortical development on conventional MRI by plain sight is often difficult owing to their subtlety and the complexity of the brain's convolutions [47]. MRI postprocessing can facilitate lesion detection. By following the

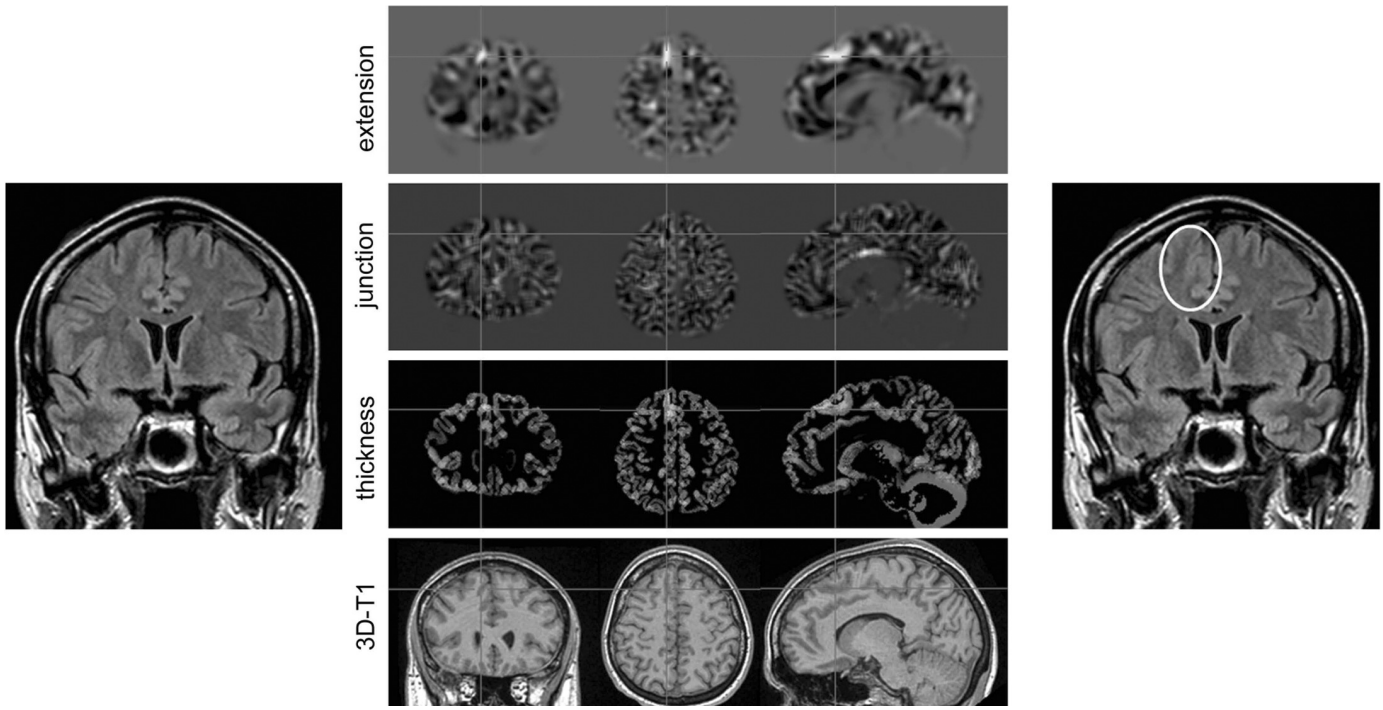

Fig. 64.13 Automated morphometric analysis of a patient with formally cryptogenic epilepsy. Repeated 1.5-T MRI was read as non-lesional (no 3-T MRI possible because of VNS). MRI postprocessing (Morphometric Analysis Program [48]) highlighted a right frontoparasagittal region, which, by invasive recordings, proved to be the seizure onset zone. After extended lesionectomy the patient is seizure free for 1.5 years. Histology: FCD IIB.

principle of voxel-based morphometry, morphometric MRI analysis allows for the objectivisation of abnormalities of cortical texture [47] or grey–white matter junction, cortical thickness or extension of cortex into the white matter [48], all of which are features of focal cortical dysplasia. By highlighting suspicious cortical regions, MRI postprocessing can guide the neuroradiologist or epileptologist for a second look and thereby increase the sensitivity of MRI evaluation. In our personal experience, patients who have been rated non-lesional for years have become seizure free after resection of an FCD identified by morphometric analysis (see Fig. 64.13). Data from the SwissEpi Center in Zurich, Switzerland, indicate that morphometric analysis may provide relevant new information regarding the presence or extent of FCD in the range of 7–8% of patients who are referred to a tertiary epilepsy centre [as compared with expert visual analysis of the same MRI; data refer to 215 patients who received MRI postprocessing at the SwissEpi Center in 2006 (personal communication, H.J. Huppertz, 2007)].

Not only FCD can be recognized through postprocessing. We recently described the value of MRI postprocessing for the detection of subcortical band heterotopia [12]. However, MRI postprocessing is still in the process of being optimized and at present is applied at a minority of epilepsy centres. Questions that remain to be evaluated over the next years are: (1) What is the yield of MRI postprocessing in 'non-lesional' patients? (2) What epilepsy relevant aetiologies can be identified by postprocessing? (3) Which postprocessing method proves effective, easily applicable and finally broadly available? From today's perspective, MRI postprocessing is a promising technique that has the potential to improve presurgical evaluation of cryptogenic epilepsy patients. Figure 64.13 shows an example of an FCD detected only after MRI post processing (method of H.J. Huppertz [48]).

MR-volumetry

Quantitative MRI evaluation of the hippocampus and amygdala can be applied as an auxiliary method in the presurgical evaluation of patients with MTLE. Especially in case of uncertainty regarding bilateral damage, it can be helpful identifying the side(s) of pathology [49]. Hippocampal volumetry aims to identify atrophy in individuals compared with a normative database. If performed by manual tracing, hippocampal volumetry is time-consuming, and intensive training is required to achieve good inter-rater reliability. However, newer studies show that automated techniques are much faster than and equally precise as manual hippocampal volumetry [50]. For hippocampal volumetry, positive prediction of histology (MTS) and surgical outcome has been shown [49].

MR-relaxometry

Like MR-volumetry, MR-relaxometry is a quantitative MRI measure that is mostly applied to the hippocampus. Estimating the transversal relaxation time on T2- or FLAIR-weighted images, it provides an objective and similar value of 'signal intensity' on those sequences. Compared with a normal database, pathological

signal increase corresponding to MTS can be identified. The method has good sensitivity and specificity for MTS, and shows a high positive predictive value not only for postoperative histology, but also for surgical outcome [49]. However, the technique is not usually applied to all patients with MTLE; it is restricted to those with suspected bilateral hippocampal pathology.

Functional MRI

Functional MRI is a non-invasive method of localizing functional brain areas. It detects subtle magnetization changes in response to local blood perfusion changes that are elicited by neuronal activation. fMRI is primarily used for the presurgical determination of language dominance and the localization of motor cortex. The fMRI-based prediction of memory outcome after temporomesial surgery is still experimental.

In the context of epilepsy surgery, the most widely used (but nevertheless not standardized) presurgical application of fMRI is the *determination of language dominance* [51]. After initial studies showed good correlation between fMRI and the gold standard Wada test, there was growing evidence to suggest that language dominance prediction may be not reliable at the individual patient level. A recent study from our group showed that even those patients with Wada test-proven atypical language dominance can show strongly lateralized fMRI [52]. Thus, discriminating between typically and atypically dominant patients and predicting the credibility at fMRI at the individual patient level often becomes impossible. Even more questionable than fMRI-based language *lateralization* is the *localization* of language function. The main pitfalls of fMRI in this context are the lack of discrimination between language-essential cortex and language use-associated cortex as well as the subjectivity of threshold determination for activated versus non-activated cortex [53].

Despite the fact that fMRI underlies continued attempts to improve its validity, it is unlikely that it can be more than a screening method for patients with clearly unilateral language dominance. If fMRI fails to show unilateral dominance, a Wada test should be applied for language lateralization. For language localization, electrical stimulation mapping remains the gold standard.

Functional MRI is also used for the identification of the motor cortex. Activation tasks are rather simple (i.e. alternating blocks of finger movement and rest to identify cortical hand representation) and cerebral activation is robust. Modern technology allows the integration of activation maps into neuronavigation systems and thereby helps neurosurgeons to identify cortical areas that should be spared from resection. However, as for language localization, there are again some critical aspects that must be kept in mind. No surgeon should choose the resection margins on the basis of the spatial extent of fMRI activation. The extent of activation is simply a function of the selected statistical threshold demarcating activated from inactive brain tissue. The choice of the threshold is arbitrary and cannot be transferred between patients or even between sessions for the same patient. Additionally, in the vicinity of cerebral lesions the fMRI results may appear as false negative or positive [54,55]. This can be due to lesion-induced susceptibility artefacts that prevent the identification of magnetization changes or impaired vascular response within lesional or perilesional tissue. Therefore, fMRI should only be used to estimate the brain area where the motor functions should be detected but direct electrophysiological verification is recommended before resection is undertaken. Figures 64.10 and 64.12 show examples of fMRI for the localization of cortical hand representation.

Less well established is the application of fMRI for the presurgical lateralization of memory functions and prediction of postsurgical memory deficits. Although some studies report favourable results [56], the method must be further evaluated to understand its reliability at the individual patient level.

Diffusion-based MRI and tractography

Diffusion-based MRI [diffusion-weighted imaging (DWI)] measures the diffusion of water molecules in different directions. A diffusion-weighted sequence calculates the diffusivity of water in at least three planes, although the number of directions is being progressively increased and leads to a more accurate estimation of the diffusion direction. Two basic parameters are used to describe the diffusivity: the *apparent diffusion coefficient* (ADC), which describes the amount of diffusion, and the *fractional anisotropy*, which describes directed diffusion. There are three emerging applications of DWI which can provide valuable information in the evaluation of an individual with epilepsy (for a review see ref. 57). One application is the identification of the seizure focus. Local ADC changes following partial seizures open up the possibility of localizing seizure onset in patients with partial epilepsy. However, the restricted data are not yet conclusive regarding the percentage of patients in whom focus localization is reliable this way. A practical problem is that diffusion changes after single seizures are only transient. Therefore, an enormous logistical effort seems necessary to enable early postictal access to MRI possible.

A more practicable application of DWI is the identification of interictal DWI abnormalities as hints of the localization and extent of epileptogenic lesions. DWI studies found abnormal anisotropy values in the epileptic hippocampus compared with the contralateral side, as well as in hippocampi of epilepsy patients compared with healthy subjects. In addition, neocortical seizure foci can be identified via DWI. Malformations of cortical development have been examined and showed reduced anisotropy and increased diffusivity. Other studies identified DWI abnormalities in MRI-negative but stereo EEG-positive neocortex (meaning the seizure onset area). Therefore, DWI might help in identifying epileptogenic lesions not detected by MRI. However, this application has not yet been sufficiently evaluated for routine application [57].

Diffusion-weighted imaging-based tractography [diffusion tensor imaging (DTI)] is used at present in clinical application. DTI is a relatively reliable method for identifing white matter pathways *in vivo*. On the one hand, visualization of fibre tracks in the vicinity of epileptogenic lesions allows one to assess the risk of resection-related neurological deficits in patients. On the other hand, including tractography information in the neuronavigation system allows neurosurgeons to adapt their resection in a way which may circumvent postoperative neurological deficits

(with regard to the pyramidal tract or the fibres of the Meyers loop). For the application of this technique in epilepsy surgery, further validation studies are required [57].

Fusion of multiple imaging techniques (including neuronavigation)

The imaging-based presurgical evaluation of complicated epilepsy patients can comprise multiple modalities such as structural imaging (MRI, DTI and MRI postprocessing), functional imaging (fMRI, PET, SPECT, MEG) and information obtained from implanted electrodes. Mentally synthesizing the results of the different modalities is essential for the epileptologist in order to draft resective surgery. Bringing this information together within a common stereotactic room for neuronavigation, however, can facilitate execution of the resection by neurosurgeons. The challenge with these procedures is that all of the information must be coregistered upon the individual patient's brain. The reference dataset for the fusion is usually an isotropic, gap-less three-dimensional T1 sequence, but isotropic three-dimensional-T2 or three-dimensional FLAIR can also be used for this purpose. If data are determined for a normalized brain (i.e. MRI postprocessing) then data must be inversely normalized. All of this is technically possible with a variety of individually programmed software tools (see ref. 58 for a neuronavigation-guided implantation of an FCD which was detected only after morphometric MRI analysis relying on the comparison of the spatially normalized individual brain with a normal data base).

However, regarding the utility of multiple image fusion one has to be aware of the fact that not everything that is technically possible is clinically reasonable. Disregarding the issue of activation thresholds for fMRI, PET, SPECT and even morphometric MRI analysis may lead to dangerous overinterpretation of imaging results [53]. The final value of multimodality fusioning for epilepsy surgery will have to be examined by future studies [58,59].

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65 PET and SPECT in Presurgical Evaluation of Epilepsy

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Introduction

A presurgical evaluation starts with a complete seizure history, physical and neurological examination, routine scalp electroencephalography and high-resolution magnetic resonance imaging (MRI) of the brain to assess structural abnormalities [1]. These investigations are complemented by video-EEG monitoring, which allows evaluation of the clinical features of seizures, interictal and ictal EEG, ictal SPECT, interictal 2-[^{18}F]fluoro-2-deoxyglucose (FDG) PET and neuropsychological examination. The aim of presurgical evaluation of patients with refractory partial epilepsy is to localize and to determine whether or not a patient has a single epileptogenic zone. The *epileptogenic zone* is the cortical region that is indispensable for the generation of seizures, and which has to be removed to render a patient seizure free. It is a theoretical construct, defined in terms of different *cortical zones* [2]. The *irritative zone* is the region of cerebral cortex producing the interictal spikes. The *seizure onset zone* is the region in which the seizures actually originate. Ictal SPECT is the only imaging modality that can define in a reliable and consistent manner the ictal onset zone. The *symptomatogenic zone* is the (sub)cortical region producing ictal symptoms. The *epileptic lesion* can be visualized on morphological imaging such as MRI. The *functional deficit zone* is the part of the cortex with an abnormal function in between seizures, due to morphological or functional factors, or both [3]. Interictal FDG-PET provides information on regions of cortex displaying decreased glucose metabolism, which usually contain, but tend to be larger than, the ictal onset zone. Epilepsy surgery has the best results if the different cortical zones are concordant, i.e. point towards the same cortical region, provided that there is no overlap with *eloquent cortex*.

PET

Methodology

PET is based upon the detection of radioligands and computerized tomographic reconstruction of the emitted annihilation rays. It permits the non-invasive measurement of the regional biodistribution of trace amounts of a radioligand and, therefore, the monitoring of its regional kinetics. The measured radioactive concentrations can be translated into colour-coded images and, with an appropriate calibration, it is also possible to quantify the regional tracer concentration at any given time.

Multiple PET tracers have been developed to visualize not only glucose metabolism, but also a wide variety of specific molecular targets such as proteins and specifically receptor systems. Various receptors have been studied in epilepsy: changes in the γ-aminobutyric acid $(GABA)_A$ receptor [4], opioid receptor [5], 5-HT_{1A} serotonin receptor [6], nicotinic acetylcholine receptor systems and others have been described. Of the receptor tracers, ^{11}C- or ^{18}F-labelled flumazenil (FMZ), which binds to the $GABA_A$ receptor, has been studied most often. The use of FMZ in patients with epilepsy, however, has the disadvantage that its binding is affected by several antiepileptic drugs that are often used in clinical practice, such as phenobarbital and benzodiazepines, making it impossible to reliably use this tracer in a large number of patients with refractory partial epilepsy. Although antiepileptic drugs (such as phenobarbital and valproate) cause a depression of glucose metabolism, this drug-induced hypometabolism is fairly uniform and does not affect the degree of asymmetry in FDG metabolism between the ictal onset zone and the contralateral cortex [7]. This is important as FDG-PET can be performed in all patients with refractory partial epilepsy, who usually take one or more antiepileptic drugs at the time of the PET study. Although FDG is available on a daily basis in a nuclear medicine department for especially oncological applications, and the superiority of studying these receptor systems over glucose metabolism in the presurgical evaluation of patients with refractory epilepsy remains to be proven [8,9], their use in clinical practice is limited at the moment. Here, we will, therefore, focus on glucose metabolism. We will also briefly discuss alpha-[^{11}C]methyl-L-tryptophan (AMT) PET, which has been useful mainly in the presurgical evaluation of patients with tuberous sclerosis complex (TSC) [10].

Measurement of glucose consumption using FDG requires an incubation period of 30–45 min after tracer administration before brain scanning (http://www.eanm.org/scientific_info/guidelines/guidelines_intro.php?navId=54). During this time, FDG is trapped and accumulates in cells as a function of glucose transport and hexokinase activity. The FDG scan, therefore, reflects cerebral glucose metabolism during the uptake, weighted towards the beginning of that period, primarily the first 10 min after injection, and may underestimate changes in metabolic rates associated with changes in cerebral function of short duration [11].

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Spatial resolution and partial volume effect

The first tomographs had an in-plane resolution of 15 mm. Current technology has reduced spatial resolution to 3–4 mm. One of the consequences of this limited spatial resolution is the so-called partial volume effect, which can be defined as an averaging of the signal between neighbouring areas. This effect concerns structures smaller than approximately twice the spatial resolution of the system, such as the cortical ribbon of the brain. It results in a blurring of boundaries between adjacent structures and, therefore, in poor definition of anatomical details, as well as in an underestimation of true radioligand concentration for smaller structures. Higher spatial resolution improves the sensitivity of PET studies as, due to partial volume effect, the apparent size of the hypometabolic zone is increased but the degree of hypometabolism is underestimated. Methods to correct for this variable have been designed and implemented (see references in ref. 12). Partial volume correction increases the sensitivity of detecting a lateralizing asymmetry of hippocampal metabolic activity by 15–20% over that without partial volume correction in patients with unilateral hippocampal sclerosis (HS) [13], and improves the detection accuracy of small hypometabolic lesions in FDG-PET images of the brain [14].

PET data analysis

Interpretation of PET images can be achieved through visual inspection alone. Quantification of PET studies may be relative (raw counts) or absolute [after kinetic modelling, to obtain, for example, glucose metabolic rates or receptor densities (B_{max})]. Measurements are obtained in regions of interest (ROI), which are affected by several sources of variations (size, shape, positioning) and biases (partial volume effect). These data are used for comparison with a control population or calculation of asymmetry indices, or normalized to global counts. Quantitative analysis can help validate or negate contradictory or questionable visual interpretation. Automated, non-interactive, voxel-based techniques, such as statistical parametric mapping (http://www.fil.ion.ucl.ac.uk/spm/) or three-dimensional stereotactic surface rendering methods, offer more objective, extensive, rigorous and detailed analysis of brain metabolic activity. Comparisons with a control group may be performed for groups of patients but also for each patient individually. Using SPM analysis of quantitative (CMRGlu) and non-quantitative (radioactive counts) data, Signorini and colleagues [15] obtained the same pattern of results and suggested that it no longer appeared justified to perform invasive arterial catheterization and blood sampling for FDG-PET scans in patients with epilepsy to obtain valuable and reliable functional information in routine clinical practice.

FDG-PET and ictal onset zone in refractory partial epilepsy

Interictal FDG-PET

The vast majority of FDG-PET studies have been carried out during the interictal state. Kuhl and colleagues [11] were the first to demonstrate that interictal FDG scans are characterized by a localized depression in cerebral glucose consumption that correlated anatomically with the EEG spike foci in patients with partial epilepsy. The metabolic defect on PET was larger than atrophic lesions found on CT scan and the structural damage was found at pathological examination. These original findings were later expanded by Engel and colleagues [16] and largely confirmed by many others [4,17–27]. More than 70% of patients with partial epilepsy show a localized area of decreased brain glucose metabolism or hypometabolism on FDG-PET. The hypometabolism may be regional or lobar and usually has a progressive demarcation from the normal cortex. It may also be more widespread and multilobar; in this case, the most hypometabolic lobe is usually the lobe of seizure onset [4]. The hypometabolic region may include an area with more severe hypometabolism and a sharp demarcation from the adjacent cortex. This metabolic pattern often corresponds to a structural lesion. The site of ictal onset usually lies within an area of hypometabolism.

The hypometabolism is usually on the side of the brain with the epileptogenic zone, but in a minority of cases, false lateralizations are possible [4,16–21]. False lateralizations may be due to postictal effects or to unrecognized, subclinical seizure activity during the uptake phase or contralateral propagation of seizures. Following complex partial seizures, the ipsilateral temporal metabolic rate is relatively increased for 48 h before falling significantly later [28].

Patients with extratemporal lobe epilepsy are less likely to have an abnormal PET study than patients with temporal lobe epilepsy (TLE) [29]. Based on a review of the literature, Spencer and colleagues [30] reported that interictal FDG-PET in TLE as judged by EEG criteria had a sensitivity of 84% and a specificity of 86%, whereas in extratemporal epilepsy sensitivity was 33% and specificity 95%. With advanced processing of FDG-PET data, this sensitivity is higher [29]. When a lesion is detected by CT or MRI, FDG-PET tends to be abnormal as well. The hypometabolic zone is larger and more extensive than the lesion itself [4,31].

Cortical dysplasia can present with either hypometabolism or displaced grey matter activity to a white matter area [32]. This latter metabolic pattern is a unique feature of cortical dysplasia and it is highly suggestive of this pathology. It represents glucose metabolism of abnormally located grey matter rather than a subclinical ictal phenomenon.

Prediction of seizure outcome on the basis of PET data is an important issue in patients with uncontrolled partial seizures, as PET results may influence patient selection for surgery. In patients with TLE, temporal hypometabolism on FDG-PET predicts successful temporal lobectomy even when surface electroencephalography and MRI are non-localizing [9,18,23,24,26,33–36]. Multilobar hypometabolism [35], or extratemporal hypometabolism [24], is associated with a higher likelihood of postsurgical seizure activity. Interestingly, it has been found that patients with thalamic hypometabolism ipsilateral to the temporal lobe seizure focus were at higher risk of postoperative seizures than were patients with no thalamic asymmetry. Furthermore, patients with relative contralateral thalamic hypometabolism were not seizure free postoperatively [37]. Normal PET scans are associated with suboptimal surgical outcome [24] and intracranial electroencephalography studies may be less likely to disclose an epileptogenic region when FDG-PET shows no hypometabolism [35]. Nevertheless, these patients without apparent hypometabolism may benefit from surgery but may need further scrutiny [38].

Initial PET studies were performed before MRI scans were available. When high-resolution MR scans became available, the added value of FDG-PET was questioned. Several recent studies, however, have stressed that FDG-PET can give additional information in the presurgical evaluation of patients with refractory partial epilepsy, which is independent of results of other investigations, such as high-resolution MRI. Carne and colleagues [33] reported good surgical results in patients with MR-negative refractory TLE and unilateral temporal hypometabolism, and suggested that MR-negative PET-positive TLE represents a surgically remediable syndrome distinct from mesial temporal lobe epilepsy related to hippocampal sclerosis (mTLE-HS), with focal hypometabolism involving primarily lateral neocortical rather than mesial temporal structures [39] (Plate 65.1). Lee and colleagues [23] reported their experience with FDG-PET in the largest series to date of surgical outcome in 89 patients with refractory partial epilepsy and normal MRI. Overall, 35 had frontal lobe epilepsy, 31 neocortical TLE, 11 occipital lobe epilepsy, 11 parietal lobe epilepsy and one multifocal epilepsy. In total, 47% of patients remained seizure free for more than 2 years after surgery and 80% had a seizure reduction of at least 90%. Diagnostic sensitivity of FDG-PET as analysed by SPM was 44%. FDG-PET localization was greatest in neocortical TLE and significantly related to seizure-free outcome. This study confirmed the usefulness of lateralized hypometabolism in MR-negative TLE. Given that patients with negative MRIs and temporal hypometabolism on FDG-PET have become seizure free following lateral temporal resections [33,40], it may be possible to develop criteria that would permit sparing of mesial temporal structures in some patients based on the results of FDG-PET. Ollenberger and colleagues [41] assessed the role of FDG-PET in the diagnosis and management of children with refractory epilepsy. A majority of their patients had extratemporal lobe epilepsy. In this retrospective study, FDG-PET studies were obtained after all other diagnostic investigations had been performed. FDG-PET provided information additional to that obtained with other investigations regarding the epileptogenic zone in 88 out of 113 patients (77%), and changed management in half of the patients. In the group of patients who were considered good surgical candidates (n = 92), FDG-PET data excluded 36 patients (39%) from surgery. However, it would be impossible to know whether or not these patients might have benefited from surgery and been denied it inappropriately because of the FDG-PET data. In the group of patients who were not considered good surgical candidates (n = 21), FDG-PET data made epilepsy surgery possible in one patient (5%). Ollenberger and colleagues [41] concluded that FDG-PET should be part of a routine work-up in all paediatric patients with refractory epilepsy who are being considered for surgery. Uijl and colleagues [9] reported that FDG-PET was most useful in patients with TLE when MRI was normal or did not show unilateral temporal lobe abnormalities, and when ictal EEG results were not concordant with MRI findings or seizure semiology. O'Brien and colleagues [42] reported that FDG-PET is cost-effective in the presurgical evaluation, particularly when used in patients with a non-localizing or non-concordant video-EEG monitoring or MRI result.

Ictal FDG-PET

In patients with frequent serial seizures or status epilepticus, ictal PET can be obtained and can demonstrate the ictal onset zone as an area of hypermetabolism, even when electroencephalography is not informative [43–45] (Plate 65.2). Occasionally, seizures occur during FDG uptake and produce a hypermetabolic area at the interictal hypometabolic focus [31].

FDG-PET hypometabolism in areas remote from the ictal onset zone

The underlying neurobiology of FDG-PET hypometabolism is not well understood, and has been ascribed to factors such as neuronal loss, diaschisis, inhibitory processes or reduction in synaptic density. The area of FDG-PET hypometabolism is often larger than the ictal onset zone and it has been suggested that this area of hypometabolism represents the functional deficit zone [2,25,46]. In mTLE-HS, the hypometabolism may extend to ipsilateral frontal and parietal cortex, as well as to subcortical structures such as ipsilateral basal ganglia and thalamus, and contralateral cerebellar lobe [20]. mTLE-HS is characterized by neuronal loss and gliosis in the hippocampus. However, there is no relation between the degree of interictal PET hypometabolism and the amount of hippocampal gliosis or cell loss [47]. Furthermore, temporal lobe hypometabolism has been observed in the absence of HS or any other identifiable pathology [23,33], suggesting that hippocampal atrophy is not a major determinant of hypometabolism. Using non-quantitative FDG-PET data normalized for white matter activity only, we correlated interictal FDG-PET metabolism and ictal SPECT perfusion changes in mTLE-HS [25]. Surprisingly, we found that *interictal* hypometabolism was greatest in the ipsilateral frontal lobe, and that this region coincided with the area of greatest *ictal* hypoperfusion, consistent with a seizure-related dynamic process (Plate 65.3). Crossed cerebellar diaschisis suggested that ipsilateral frontal lobe hypoperfusion/metabolism represented strong inhibition during complex partial seizures [48]. We formulated the hypothesis of surround inhibition, which is a dynamic (i.e. seizure-related) process, present in seizure propagation pathways, and which is a defence mechanism against seizure propagation. It is characterized by *interictal* hypometabolism and *ictal* hypoperfusion, and may be responsible for interictal and ictal functional deficits that may be reversible upon cessation of seizure activity. In this hypothesis, some interneurones in the hyperperfused temporal lobe undergo active synaptic inhibition with downstream decreased synaptic activity in the ipsilateral frontal lobe [48], which is the most common route of spread of mesial temporal lobe seizures [49]. This hypothesis might explain why ipsilateral frontal lobe excitability, as measured with transcranial magnetic stimulation, in patients with refractory TLE correlates strongly with time to next seizure [50]. Ictal surround inhibition has been shown to be present in the cortex surrounding an epileptic focus using optical imaging, which is a functional imaging modality based on the same principle of coupling of focal alterations in metabolism and blood flow [51]. A decrease in the optical signal correlated spatially with a decrease in neuronal activity recorded from cortex surrounding an epileptic focus. Witte and colleagues [52] reported PET findings of a patient who had a seizure during PET scanning and documented that the transition from interictal to ictal activity was

accompanied by the development of a hypermetabolic epileptic focus and the dynamic enlargement of surrounding hypometabolism (see also Plate 65.2).

Clinical correlations with FDG hypometabolism in areas remote from the ictal onset zone

FDG-PET hypometabolism has been related to neuropsychological and psychiatric dysfunctioning in epilepsy. McDonald and colleagues [53] correlated interictal FDG-PET with frontal lobe executive function, and found that resting frontal lobe metabolic values were strong predictors of executive functioning in patients with epilepsy. Jokeit and colleagues [54] reported a correlation between prefrontal metabolic asymmetry with frontal lobe cognitive deficits in patients with TLE. Takaya and colleagues [55] compared cognitive functions and interictal cerebral glucose metabolism of 11 patients with mTLE and frequent seizures to those of 10 patients with mTLE and rare seizures. The frequent-seizure group had more set-shifting impairment that correlated with glucose hypometabolism in the prefrontal cortices. These results suggested that frequent seizures in mTLE are associated with hypofunction of the prefrontal cortex. Salzberg and colleagues [56] reported that patients with TLE and a history of depression at any time preoperatively showed focal hypometabolism in ipsilateral orbitofrontal cortex compared with those who did not.

FDG hypometabolism in areas remote from the ictal onset zone is seizure-related and reversible

Several reports provide evidence that hypometabolism at a distance from the seizure focus may disappear on seizure remission. Akimura *et al.* [46] described improvement in hypometabolism of ipsilateral areas remote from the ictal onset zone, mainly the frontal lobe, in patients who underwent temporal lobectomy. Spanaki and colleagues [57] documented increases in metabolism in the ipsilateral inferior frontal lobe and thalamus after temporal lobectomy for intractable TLE. Joo and colleagues [58] compared pre- and postoperative FDG-PET scans in patients with mTLE-HS who were rendered seizure free after surgery. Increases in FDG metabolism after surgery were seen in the propagation pathways of ictal and interictal epileptic discharges, for example temporal stem white matter, inferior precentral gyrus and anterior cingulate gyrus in the ipsilateral hemisphere, suggesting that hypometabolism in these regions was functional, seizure related and reversible. On the other hand, decreases were seen in brain structures with afferents from resected anterior mesial temporal structures.

Clinical correlations of resolution of FDG hypometabolism in areas remote from the ictal onset zone after seizure remission

A key question is whether or not disappearance of FDG-PET hypometabolism at a distance from the ictal onset zone after (postsurgical) seizure remission correlates with neuropsychological and neuropsychiatric improvement, which is common after successful epilepsy surgery [59,60]. In the presurgical assessment, attention is focused on eloquent cortex and loss of function after epilepsy surgery. It is equally important to counsel the patients what they could gain in terms of cerebral functioning after successful epilepsy surgery. Large studies correlating neuropsychological and neuropsychiatric improvements with disappearance of FDG-PET hypometabolism in areas at a distance from the resection site have not been performed and are warranted. To illustrate this point, we provided anecdotal evidence that cognitive impairment associated with frontal lobe hypometabolism due to ongoing parietal lobe seizures recovered over more than 1 year after remission of seizures, and this improvement was associated with resolution of hypometabolism [45] (Plate 65.2).

AMT-PET in refractory partial epilepsy

Tuberous sclerosis complex (TSC) is an autosomal dominant disease in which multiple cortical tubers or focal cortical dysplasias are a primary hallmark. Seizures are the most common symptom of the disease and either infantile spasms or West syndrome is particularly frequent during the first several years of life. Because of the multitude of cortical lesions, however, identifying the epileptogenic tuber(s) is difficult. Chugani and colleagues [10] reported that epileptogenic tubers have an increased AMT uptake and AMT-PET differentiates between epileptogenic and non-epileptogenic tubers in patients with TSC. AMT-PET localization is mostly seen in patients with frequent interictal abnormalities on the EEG [61]. Focal increase of cortical AMT uptake is less sensitive but more specific for the lobe of seizure onset than corresponding FDG-PET hypometabolism, and is often associated with epileptogenic cortical developmental malformations in children without TSC. AMT-PET can assist placement of subdural electrodes even when MRI and FDG-PET fail to provide adequate localizing information [62]. Kagawa and colleagues [63] analysed the surgical outcome of children with TSC in relation to AMT-PET results. Their findings suggested that resection of tubers with increased AMT uptake is highly desirable to achieve seizure-free surgical outcome in children with TSC and intractable epilepsy.

SPECT

Methodology

Ictal SPECT has the potential to localize the ictal onset zone accurately in a non-invasive manner. In order to reliably deliver early ictal SPECT injections, detailed attention should be paid to the logistics of ictal SPECT set-up. Ictal SPECT injections should be performed in the video-EEG suite, with the nursing and review station close to the rooms of the patients. Medical personnel should be educated in handling of radioligands and must be familiar with the electroclinical features of epileptic seizures. The brain perfusion agent should be available in the room and the injection system should allow for fast ictal injections [64,65]. High-resolution SPECT and MR scanners should be available. An excellent cooperation between the neurology and nuclear medicine department is of crucial importance. If the implementation of ictal SPECT is too difficult then referral of selected patients for ictal SPECT should be considered.

SPECT studies in partial epilepsy have been carried out with blood flow tracers, which are $^{99}Tc^{m}$-labelled compounds, such as $^{99}Tc^{m}$ hexamethyl-propyleneamine oxime ($^{99}Tc^{m}$-HMPAO) or $^{99}Tc^{m}$ ethyl cysteinate dimer ($^{99}Tc^{m}$-ECD). These lipophilic amines rapidly cross the blood–brain barrier (up to 85% of brain uptake on the first pass). Once inside the brain they form a hydrophilic compound that is trapped within cells, which prevents washout.

Cerebral uptake is complete within 2 min and less than 5% is redistributed later. The activity in the brain remains essentially constant and proportional to regional perfusion at the time of administration. Its distribution is not affected by subsequent changes in cerebral blood flow (CBF) or pharmacological intervention. Given the long half-life of these radiopharmaceuticals and very slow regional redistribution, static SPECT scans can be acquired up to 4 h after their intravenous administration during a seizure [66]. During the initial ictal studies in epilepsy, $^{99}Tc^{m}$-HMPAO had to be reconstituted rapidly at the bedside during a seizure [67], which made the implementation of ictal injections of $^{99}Tc^{m}$-HMPAO more difficult than with $^{99}Tc^{m}$-ECD, which is a stable ligand, and which allowed for earlier ictal injections. A stabilized form of $^{99}Tc^{m}$-HMPAO is now available. $^{99}Tc^{m}$-ECD is cleared from the body more rapidly than $^{99}Tc^{m}$-HMPAO, giving a higher brain/background ratio of activity and a superior SPECT image quality [68]. These SPECT radiopharmaceuticals can be prepared any time, without the requirement of running a complex cyclotron. The kinetic profile of these tracers with fast uptake and stable retention allows for injecting the patient at distance from the SPECT camera, for example in the epilepsy monitoring unit, during a seizure, which is a major advantage. Scanning is then carried out when the patient has recovered full consciousness and is able to collaborate.

The localizing value of ictal SPECT performed with cerebral perfusion imaging agents in patients with partial epilepsy is based on cerebral metabolic and perfusion coupling, i.e. an increase in neuronal metabolic activity is associated with an increase in CBF, and a decrease in neuronal metabolic activity with a decrease in CBF.

Ictal SPECT is obtained by injecting the ligand during a seizure and an interictal SPECT by injecting the ligand between seizures. The accuracy of ictal SPECT analysis is highest when comparing the ictal with interictal perfusion data. Methodologically, this can be carried out by traditional side-by-side visual evaluation, but computer-aided voxel-based co-registration techniques (such as subtraction ictal SPECT co-registered to MRI (SISCOM) [69,70] and ictal–interictal SPECT difference image (ISAS) [71]) are fast, more accurate and objective, and are routinely available. For SISCOM analysis, interictal and ictal SPECT scans are co-registered using an automatic registration algorithm based on mutual information [72] and the interictal image is then subtracted from the ictal. The difference image is smoothed and transformed into a *z*-score map using the mean and the standard deviation of the differences in all brain voxels. The mean image of the ictal and interictal coregistered images can be used for coregistration to the patient's MRI. The same transformation is then applied to the z-map. For the functional overlay different thresholds can be used to assess most significant differences. Careful quality control of registration (e.g. assessment of acquisition movement artefacts, registration errors) and subtraction is important in order to avoid false-positive and false-negative results, and the result of the SISCOM analysis has to be concordant with the result of visual comparison of the ictal and interictal images, and other data of the presurgical evaluation. Furthermore, SISCOM may be false-negative due to subclinical seizure activity at the moment of tracer injection of interictal SPECT imaging [73]. Electroencephalography monitoring during the interictal injection, therefore, should be routinely performed.

Ictal SPECT in presurgical evaluation

The interpretation of ictal SPECT images should always be undertaken in the context of a full presurgical evaluation. The injection time should be known, as early injections give the best results. The importance of early tracer injection after the beginning of the seizure cannot be overemphasized. It has been shown that an injection delay of less than 20 s is significantly correlated with a correct localization [73]. With early injections, the largest and most intense cluster is more likely to represent the seizure onset zone, and not seizure propagation. Several propagation patterns have been described. Propagation is often from posterior brain regions (parieto-occipital lobes) to anterior brain regions (temporal and frontal lobes) [74]. Noachtar and colleagues [75] reported propagation in 85% of parieto-occipital epilepsy. Another propagation pattern is from the temporal to the frontal lobe. In patients with a temporal lobe lesion on MRI and discordant frontal lobe seizures, ictal SPECT may show propagation from temporal to frontal lobe, obviating the need for invasive monitoring. Propagation from one temporal lobe to the contralateral temporal lobe has been reported in around 1% of cases [21]. Propagation of ictal activity can partly explain why a high SISCOM threshold has a lower sensitivity and higher specificity than a low threshold, which has a higher sensitivity but lower specificity [76]. In clinical practice, using different SISCOM thresholds can help elucidate propagation patterns. In partial epilepsy caused by single MRI-visible focal dysplastic lesions (FDLs), we reported three different ictal perfusion patterns [77]. The first pattern was characterized by the largest and most intense hyperperfusion at the FDL, and was most often seen with very early injections, and represented the ictal onset zone before seizure propagation occurred. The second pattern was characterized by an 'hourglass pattern', with the least intense lobule overlapping with the FDL, and the most intense at a distance, representing propagation (Plate 65.4). Third, a variant of the second pattern showed a more complicated multilobulated propagation pattern that was most often seen in frontal lobe seizures with fast seizure propagation and relatively later ictal injection times.

The injected seizure type and ictal semiology should be known for a correct interpretation of ictal SPECT. In our hands, ictal SPECT during simple partial seizures gave no information in around 40% of cases. For this reason, we have limited the use of self-injection ictal SPECT, as this was often during isolated simple partial seizures [78]. Complex partial seizures give the best results, and secondarily generalized seizures may give multiple regions of hyperperfusion [79].

The duration of the injected seizure is important in the interpretation of ictal SPECT studies. After injection in an arm vein, the tracer takes around 30 s to reach the brain. The postictal switch, i.e. switch from ictal hyperperfusion to postictal hypoperfusion, occurs about 1 to 2 min postictally in temporal lobe seizures [80] but is shorter in extratemporal seizures. It has been estimated that extratemporal seizures should last at least 10 to 15 s after ictal SPECT injection to give localizing information [76].

O'Brien and colleagues [69] reported localization in 39% using side-by-side visual inspection versus 88% localization using SISCOM. A meta-analysis of SPECT brain imaging in patients with TLE showed a sensitivity of ictal SPECT localization of 0.97,

relative to diagnostic evaluation without imaging, while this was only 0.44 for interictal SPECT localization [81]. Interictal SPECT perfusion imaging on its own, therefore, seems to be inefficient in localizing the seizure onset zone and should be used only as a baseline perfusion measure in the comparison of ictal perfusion images. Ictal SPECT studies of complex partial seizures of extratemporal lobe origin also have an excellent localizing value, but may be more difficult to obtain when the seizures are brief in duration [82,83]. The sensitivity of ictal SPECT in extratemporal seizures has been reported to be around 90%. Ictal SPECT, and in particular SISCOM images, are predictive of postsurgical outcome [69] independently of MRI or scalp ictal EEG findings [84].

Multimodality imaging

Several imaging modalities with different spatial and temporal resolutions are available to study the brains of patients with epilepsy *in vivo*. Combinations of these imaging modalities that integrate the strengths of modalities and at the same time eliminate one or more weaknesses of an individual modality may provide new information that is superior to the information provided by each individual imaging modality (Plate 65.5). Although SISCOM is routinely performed, co-registration of ictal perfusion SPECT, interictal FDG-PET, structural MRI, functional MRI, diffusion-tensor imaging (DTI), EEG and magneto-encephalography (MEG) in one multimodality imaging platform could provide a very powerful tool to systematically study the relationships between the epileptic lesion (MRI), irritative zone (MEG and interictal EEG), ictal onset zone (ictal perfusion SPECT, ictal EEG and interictal FDG-PET), functional deficit zone (FDG-PET), eloquent cortex (fMRI and diffusion tensor tractography) and the connectivity between the different cortical regions (diffusion tensor tractography). Knowlton summarized the mounting evidence that multimodality imaging combining FDG-PET, ictal perfusion SPECT, and MEG in combination with MRI is increasing the number of patients being considered for epilepsy surgery without the need for invasive EEG studies [85]. Lee and colleagues [23] investigated patients with cryptogenic neocortical epilepsy with FDG-PET, ictal perfusion SPECT, interictal and ictal EEG, and found that concordance with two or more presurgical evaluations was significantly related to a seizure-free outcome. Chandra and colleagues [86] used the coregistered combination of FDG-PET, MRI and DTI to distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex. Compared with non-epileptogenic tubers, epileptogenic tubers had larger volumes of FDG-PET hypometabolism and increased apparent diffusion coefficient.

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66 Experimental Neurophysiological Techniques

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Introduction

There have been many advances in structural imaging over the last two decades which have greatly enhanced the processes of presurgical evaluation. We have already seen considerable advances in associated functional imaging techniques, such as positron emission tomography (PET), interictal and ictal single photon emission computerized tomography (SPECT) and magnetoencephalography (MEG), described elsewhere. This chapter outlines the principles and current or future potential applications of two specific functional imaging techniques based on computational analysis of the electroencephalogram (EEG) ictal and interictal signals, which are source modelling and EEG-correlated functional MRI (EEG/fMRI).

Source modelling of electroencephalography

More than 50 years ago, Marie Brazier [1] proposed the application of physical and mathematical principles to the localization of EEG sources based on the assumption that an active current source within a finite conductive medium will produce volume currents that lead to potential differences on the surface. In this chapter, we will first review the methodological aspects of EEG source modelling methods then examine the results for interictal spikes, and their relation to other data such as MRI or PET, and invasive recordings. Finally, we will assess the peculiar difficulties encountered in modelling ictal discharges and examine the overall clinical relevance of EEG source modelling results in the presurgical evaluation of epileptic patients. In what follows the term 'generator' refers to the anatomical structure generating the events, whereas the word 'source' refers to the modelled generator.

Methodological aspects

Principle

EEG source modelling is based on an interactive statistical estimation of the locations, orientations and amplitudes of the intracerebral generators from surface signals and this requires models for both generators and conductive media.

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Modelling the sources of interictal spikes

The easiest way to represent a current source is with a current dipole, which is produced when an ion flow through the neuronal membrane occurs at the synaptic cleft during postsynaptic excitation or inhibition of pyramidal cell dendrites and this flow is counterbalanced by a current stream along the postsynaptic membrane; this results in a group of negative and a group of positive charges, separated by a small distance along the axis of the pyramidal cell (i.e. a dipole). If a sufficient number of focal neurones are synchronously activated, as occurs during an epileptic spike, currents may be obtained with sufficient amplitude to produce a measurable potential difference at the surface because pyramidal cells are organized in columns orientated perpendicular to the cortical surface. The geometry of neuronal aggregates is of particular importance; 'closed field' configurations (i.e. groups of neurones with radial or random orientations of their dendritic trees (as in amygdala or thalamus) will theoretically give rise to very small or nil equivalent dipoles with no recordable electrical potential outside, but the activity of neurones that are orientated in a parallel way ('open field', as is for most cortex) can be modelled by an equivalent dipole, representing the vectorial sum of each of the unitary dipoles [2].

The potential to detect spikes thus heavily depends on the configuration of the generators, but also on their spatial extent and depth. For instance, the question of whether or not spikes originating solely from mesial temporal structures are detectable on the scalp surface, which is crucial for presurgical evaluation of temporal lobe epilepsies, has been much debated in the literature. A few studies suggested that mesial temporal spikes are detectable on the scalp [3–5], but this was without direct validation by intracranial recordings. Combined depth EEG and surface recordings showed that intracranial spikes involving solely the deepest mesial contacts in TLE are hardly visible on the surface [6,7].

Modelling the conductive volume

The potential differences recorded at the scalp also depend on the different conductivities of the tissues through which neuronal currents are flowing. A model for the head, therefore, has to describe mathematically the physical properties of brain tissues and liquids, i.e. the brain itself, cerebrospinal fluid (CSF), skull and scalp. In order to simplify this calculation, it is usually assumed that all of these properties are purely resistive. The geometry of head models used for dipole modelling is either spherical or realistic.

The spherical model of the human head includes concentric spherical shells of different conductivity, representing the scalp, skull, CSF and brain [8]. Although a sphere is quite well adapted to the shape of the brain over central regions, the real shape of the head is clearly different from a sphere in occipital, frontal or basal regions, which could potentially give rise to localization errors [9]. To improve the localization of intracerebral sources, realistic models of the head have been proposed [10–13], based on the extraction of scalp, skull and brain surfaces from individual MRI data.

The realistic models are generally more computationally demanding and thus less employed in clinical settings. Those realistic models are subdivided into boundary and finite element method (BEM, FEM) models [14]. BEM models use triangulation of the interfaces between compartments of equal isotropic conductivities as a geometric model. In contrast, FEM models tessellate the whole volume and allow the consideration of individual anisotropic conductivities for each element. In practical terms this implies that, in contrast to the BEM model, the FEM model can take anisotropies into account. However, since tissue conductivity is hardly measurable *in vivo*, the advantages of the FEM model are not yet fully exploited. The theoretical benefit of using realistic models instead of spherical models has been shown in recent studies [15,16], showing less localization bias in the anterior frontal lobe. Nevertheless, direct evidence of the clinical relevance of such models is still lacking. In a large study involving 100 patients (46 involving the temporal region and 54 the extratemporal region), Scheler *et al*. [17] demonstrated systematic differences in spike localization using a BEM model compared with a three concentric layers spherical model. Mean localizations were 5.9 mm more caudal and 11.7 mm more inferior with the BEM than with the spherical model. However, the spike sources were equally scattered with both models, showing that the use of the BEM model did not help to delineate a more spatially confined area.

The forward and inverse problems

If, at a given time, the source distributions and configurations within the brain as well as the conductive properties of the tissues are known, the resulting potentials at the scalp surface can be calculated on the basis of physical principles. This is generally referred to as the 'forward problem' and has a unique solution. Conversely, dipole modelling methods search for the location of intracerebral generators whose activity might explain scalp potentials, and this is referred to as the 'inverse problem'. Because each dipole is characterized by three spatial location parameters (Cartesian x, y, z or spherical r, theta, phi, co-ordinates), and three vector parameters (sense, direction and amplitude), the inverse problem is equivalent to an estimation of these parameters in a system involving $6*N$ unknowns for N generators.

As potentials are recorded at only a finite number of sites on the scalp, it is theoretically possible to obtain an infinite number of intracerebral source configurations for a given surface potential distribution. In practice, however, knowledge of the underlying pathology and physiology allows for the definition of some constraints, which considerably help in reducing the number of solutions (for example, sources cannot be located in the ventricles, white matter, eyes, etc.). Dipole inverse solutions are calculated by an iterative process in which the dipole location, orientation and amplitudes are changed step by step to obtain the best fit between the real scalp potential distribution and the theoretical distributions predicted (the solutions of the individual forward problems). The quality of the solution is evaluated by 'goodness-of-fit' or 'residual variance' parameters, respectively reflecting the percentage of data variance explained or left unexplained by the model.

Preprocessing the data

Spike averaging

Interictal spikes usually occur over the background EEG (or MEG) activity, which acts as noise and potentially contaminates the real spike topography. To increase the signal–noise ratio, spikes can be averaged but, since spikes are often polyphasic, averaging has to be triggered from the same time reference so that phases from different polarities are not cancelled. Although spike averaging is used often, this technique has been criticized for the risks of mixing spikes from different generators. The averaging of spikes from different foci gives a composite spike and can falsely suggest a spreading process by blurring the localization process [18,19]. In our experience, however, non-averaged (even filtered) spikes are difficult to model and, in most cases, a dipole solution can be obtained only around the maximal amplitude peak. Another advantage of averaging is that it may reveal small voltage deflections during the paroxysm that would otherwise be indiscernible, but it remains a risky procedure and requires careful checks on the similarities of the spikes selected.

Averaged-spike topography

Averaged spikes are usually characterized by several phases with inverse polarity. The typical deflections observed are an early positive peak, a main negative peak and a late positive peak sometimes followed by a negative wave. Analysis of the temporal sequence of voltage maps during the interictal spike can help to understand better the spatiotemporal dynamics and to formulate hypotheses regarding the underlying generators. For example, a 'dipolar' distribution of voltage fields at the scalp surface, i.e. two maxima of inverse polarity, can be considered to be from a source tangential to the scalp surface, localized approximately under the zero potential line. In a similar way, a topography characterized by a single polarity maximum at the surface suggests a source orientated radial to the scalp surface, localized under the voltage maximum itself. In the example provided in Fig. 66.1, the topographies during the main and late phases of the spike are similar, suggesting that the same generator(s) might be active during both phases. Conversely, during the early peak, as the topography differs, different sources may be active.

The evolution of the topography during the averaged spike has been evaluated with several mathematical parameters (such as the global dissimilarity index) that provide clues to segment statistically the different components of the spike [20]. Other methods using blind source separation such as independent component analysis (ICA) do not need averaging of the spikes. ICA is a technique to separate statistically independent components from a mixture of data. ICA algorithms might be helpful to isolate epileptiform discharges from background EEG [21]. Preliminary clinical studies show that source localization based on ICA

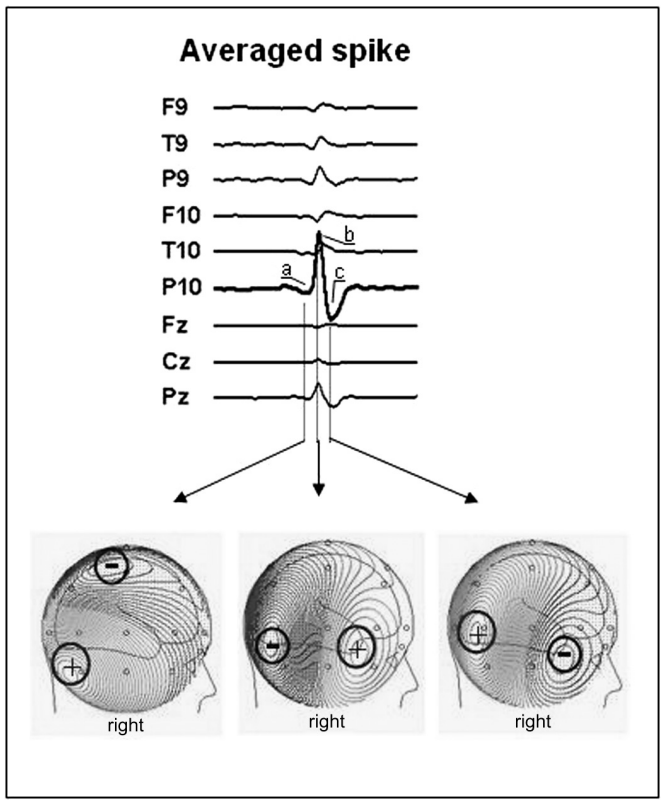


Fig. 66.1 Topographical analysis of an averaged interictal spike. Averaging is time-locked to the main negative peak of interictal spikes. The averaged spike is usually made of three or four phases with inverse polarity: (a) an early positive peak, (b) a high-amplitude negative peak, and (c) a late positive peak, sometimes followed by a negative slow-wave. The scalp voltage distribution observed at these different peaks alludes to the number of underlying generators. In this example, voltage maps at the main and late peaks are almost identical, suggesting that the same source is activated during both phases. In contrast, the early peak voltage map is clearly different, suggesting that another source might be active during this period.

decomposed spatiotemporal components appears promising for the estimation of epileptic sources, with minimal dependence on subjective decisions in the process analysis [22,23].

Dipoles modelling of interictal spikes

Instantaneous dipoles

The most simple dipole modelling approach is to estimate the instantaneous equivalent dipole that best fits the scalp voltage distribution at a single point. This method will have reasonable accuracy only if the actual generator is very focal and simple in space and over time, otherwise the solution will merely estimate the centre of mass for the activated area. The major limitations are (1) to assume that those equivalent sources are well separated, without time overlapping; and (2) to choose the time points within the spike complex of which the sources are to be calculated, ignoring other parts of the signal that might be of physiological interest.

Single equivalent dipole analysis can also be applied to time intervals, producing a pattern of multiple sequential sources (as many as the number of sampling points in the interval), which vary in location and orientation: the 'multiple instantaneous fit', or 'moving dipole' (Plate 66.1). This pattern can be interpreted as reflecting the sequential activation of multiple brain regions, limited in space and time, but the question arises as to whether or not the whole sequence of dipoles is relevant or not with regard to the anatomical propagation of transients.

When a large group of spikes is recorded in a patient, the scattering of sources may be computed mathematically to provide an estimate of the spatial extent of the interictal network. For example, Fischer *et al.* [24] calculated interictal activity extent using an ellipsoidal volume based on principal component analysis of the coordinates of all spikes. Applying this method to MEG data in patients who had undergone surgical resection, these authors demonstrated that a high coverage of this ellipsoidal volume by the resection correlated with a favourable outcome. However, this method does not estimate the extent of each source but rather the scattering of all sources.

Multiple spatiotemporal dipoles

The 'spatiotemporal approach' takes into account the course of the signals as a whole instead of considering each time sample separately. This method, first described by Michael Scherg [25], is based on the assumption that a single spike may reflect the activities overlapping in time of several 'static' dipolar sources, fixed in position and orientation, but varying in magnitude over the time interval of interest. A 'spatiotemporal dipole solution' thus characterizes the position and orientation of the sources, as well as their activation timing during the event (Fig. 66.2). The underlying concept is that if the earliest part of the spike is more likely to reflect the activity of a single source rather than the peak, this early source may also contribute to the genesis of the later time segments of the spike.

Dipole modelling strategy

In practice, it can be useful to combine dipole modelling approaches. The 'single moving dipole' approach provides a pattern of dipolar sources often grouped into 'clusters' for the time interval under consideration. This allows the estimation of both the number of active sources and the timings of their maximal activity. Next, in order to take into account the spatiotemporal evolution of the paroxysms, static dipoles with fixed location and orientation but time-varying activity are useful. In practice, a first source is fitted over the early phase of the spike, then a second is fitted to model the main peak and the residual signal unexplained by the first; this procedure can be repeated at increasing intervals from spike onset until an acceptable fit is achieved with a minimal residual variance (Fig. 66.2).

Projection of sources onto three-dimensional MRI represents the final operation of dipole modelling. The frame of the dipole model is defined by orthogonal axes passing through vertex (Cz electrode, vertical *z*-axis), right ear (T4, lateral *x*-axis) and frontopolar (Fpz, anteroposterior *y*-axis) electrodes. Co-registration of dipole modelling and anatomical data implies that both are in the same frame, which may be done by calculations using external landmarks, or by estimating the mean location of the model centre with respect to anatomy [26]. Most available software packages now allow for automatic registration of dipole modelling results onto individual or averaged MRI data.

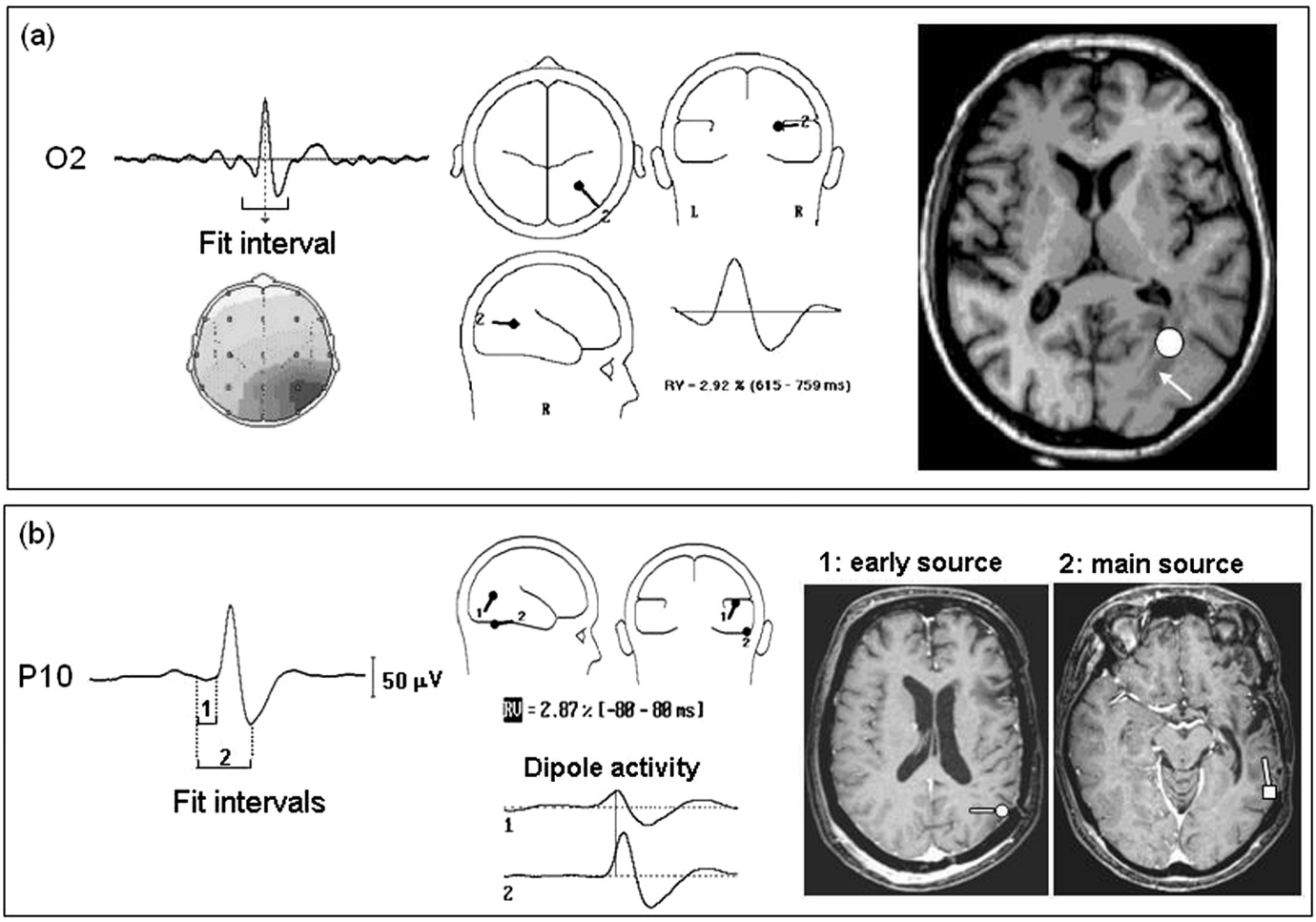


Fig. 66.2 Simple versus complex interictal spikes. In this patient with right parieto-occipital epilepsy, voltage maps at different peaks of the averaged interictal spike show identical scalp distributions. (a) This type of spike can be explained by a single source and adding others does not improve the residual variance. This source was concordant with the MRI, which showed grey matter heterotopia located in the right occipital white matter (arrow). (b) Two distinct sources are necessary to properly explain the spikes in this patient with extensive frontotemporal atrophy of the right hemisphere. They activate sequentially, and suggest early involvement of the temporoparieto-occipital junction, followed by involvement of the posterior temporal neocortex. In this case, when an additional source was added, it always converged towards the main source.

Volumetric methods

The main limitation of the equivalent dipole model is that the neuronal sources of spikes are modelled with a few dipoles that do not provide information on the spatial extent and configuration of the generators.

To overcome this intrinsic limitation, the most basic approach consists of distributing regional dipoles over a predetermined volumetric grid, which usually consists of sources lying on the cortical surface [27,28]. Following segmentation of the MR volume, dipolar sources are regularly placed along the surface of the cortical mantle [27,29]. A realistic representation contains in the region of 10 000–100 000 dipole 'pixels' (Plate 66.1c). Resolution of the inverse problem thus requires the use of either explicit or implicit constraints on the allowed current source distributions. Those constraints can be anatomofunctional (and thus based on known localization priors for the patient) or purely mathematical (based for example on the spatial configuration of the sources). Statistical approaches have been proposed to estimate the probability of sources being at a given location [29].

In the last years, other approaches based on radar applications such a spatial filtering methods (Plate 66.1b) have been proposed [30]. Source reconstruction is achieved by first defining a source space formed by a volumetric grid of target locations. For each target location, a set of beam former weights is then determined, forming an optimum spatial filter for that location and suppressing activity arising from other regions. Computing the beam former output for each location independently allows for the reconstruction of multiple (uncorrelated) sources without making prior assumptions about the total number of active sources [31]. One interesting feature of these methods is that data can be analysed in the time or in the frequency domain [30]. Thus, the spectral characteristics of the spikes can be emphasized to locate their neural sources.

Despite their attractiveness, those alternatives to classical dipole modelling approaches providing a more realistic picture of the spike sources have not yet been formally compared against older methods. Preliminary data show that some distributed source models might have sufficient resolution to delineate precisely epi-

leptic foci [32,33] but validation studies with intracranial recordings are scarce [5]. In the same vein, spatial filtering of spikes seems a promising technique but add-on value over classical approaches needs further evaluation [34].

Very few studies have evaluated exhaustively the extent of the interictal volume determined by the method. However, no gold standard is currently obtainable *in vivo* to validate hypotheses regarding those volumes. Moreover, the 'distributed-ness' of a solution might result both from the effect of the true extent of the source and the inexactness in modelling complex sources. In a simulation study of realistic spikes by Grova *et al.* [35] it was shown that some inverse methods (based on LORETA, 'low resolution brain electromagnetic tomography', or on 'maximum entropy on the mean' [36]) were able to accurately recover sources of different spatial extents, with the exception of sources in temporomesial and frontomesial regions [37]. However, several spurious sources were generated by those methods, whereas methods using MSP (multivariate source prelocalization) [38] always located very accurately the maximum of activity but not its spatial extent.

Quality of solution, accuracy of localization and validation

Quality of solution

The quality of the solution is usually assessed in terms of 'residual variance' or 'goodness of fit', but these are difficult to interpret without a reliability threshold and it is important to use other criteria. For example, the stability of the solution should be systematically taken into account by checking that (1) for one given spike, dipole results are stable as the modelling process is replayed using different starting points prior to fit and (2) for a given patient, different spike averages with similar scalp distributions yield similar dipole configurations. The existence of interactions is another criterion that should be considered. Sources are interacting when they tend to converge on the same location and display a very similar activity waveform during the fitting process, in which case only one is sufficient to explain the data (Fig. 66.2). The limitation of equivalent dipole models for large and geometrically complex spike sources has been shown by a simulation study by Kobayashi *et al.* [39]. The authors showed that a large generator area can be well modelled by a single-dipole source, and also that a small value of residual variance is not appropriate as proof or even an indication that source is small, in the clinical application of dipole modelling.

While determination of 'residual variance' is without doubt useful, it does not reflect the quality of the model used to solve the problem. For instance, the goodness of fit is usually increasing when using more dipole generator sources to model one single spike. The number of real epileptic sources is unknown, so that other estimation parameters are needed to obviate this difficulty. A recently introduced strategy to help quantify the probability of a source solution is the confidence ellipsoid volume calculation [40]. The smaller the confidence interval, the greater is the probability that the dipole resides at the fit location. The confidence volume has been shown to depend on the signal ratio of the spikes and might constitute an index of the reliability of the solution. Unnecessary spike sources in a multiple source solution might therefore lead to large confidence volume.

Accuracy of localization

Error measurements would require reference information as to the actual source locations and this is seldom the case in relation to epileptic paroxysmal transients. In some cases, error may be calculated directly by modelling simulated data from known sources, or alternatively by creating current dipoles between two adjacent intracerebral electrodes *in vivo*. The results of such studies are summarized in Table 66.1. A mean localization error of around 10 mm may be accepted [41–44], but this can vary from a few millimetres to as much as a few centimetres. Indeed it is generally well accepted that the localization error (1) is larger when the source is located deep [44–46]; (2) is smaller when realistic head models are used, compared with spherical models [45–47]; (3) is smaller when the spatial sampling of EEG electrodes or MEG captors is increased [15,48,49]; and (4) decreases when the signal–noise ratio increases. Knowing this, it is reasonable to hold that superficial dipoles calculated from 32-channel data with a good signal–noise ratio, in a realistic head model, can be localized with an error of about 5 mm.

Table 66.1 Localization errors with dipole modelling.

(a) Mean errors or range.

Reference	Localization errors
Smith *et al.* [41]	<20 mm
Cohen *et al.* [42]	10 mm (max 17 mm)
Cuffin *et al.* [43]	11 mm (max 28 mm)
Mosher *et al.* [45]	25 mm
Cuffin [48]	2–17 mm
Yvert *et al.* [46]	5–6 mm
Cuffin [44]	10.6 mm

(b) Mean errors according to mesiolateral localization of sources.

Reference	Error	
	Superficial sources	Mesial sources
Mosher *et al.* [45]	20 mm	35 mm
Yvert *et al.* [46]	5–6 mm	15–25 mm
Cuffin *et al.* [44]	9 mm	13 mm (ns)

(c) Influence of electrode number.

Reference	Number of electrodes	Error improvement
Mosher *et al.* [45]	37 versus 21	10 mm
	121 versus 37	5 mm
Yvert *et al.* [46]	32 versus 19	3 mm
	63 versus 32	1 mm
Krings *et al.* [47]	41 versus 21	5 mm

(d) Improvement in localization error according to the type of head model used.

Reference	Realistic versus spherical: error improvement
Cuffin *et al.* [48]	2.6 mm
Leahy *et al.* (phantom) [49]	0.4 mm
Crouzeix *et al.* [15]	2.5 mm (superficial sources) 12 mm (deep sources)

Validation studies

It is noteworthy that the above estimations are derived from simulated data. For physiological signals such as epileptic spikes, the locations of dipole sources can be validated when scalp and intracerebral signals are recorded simultaneously. Here, intracranial spikes can be used as triggers for averaging the corresponding scalp signal, which in turn can be modelled. Dipole localization can then be compared with intracranial electrodes in which spikes are maximally recorded. Using this technique, Lantz *et al.* [50] could identify different intracranial distributions associated with temporal scalp EEG spikes. Spikes with similar distributions were averaged together with the concomitant scalp EEG activity and the authors showed that the analysis of scalp-averaged activity allowed for the separation of different types of intracranial distributions, and the identification of the temporal regions involved during the paroxysm. Dipole locations, however, were difficult to assess because there was no projection onto MRI. This averaging technique was also used to analyse the scalp EEG signals associated with interictal mesiotemporal spikes recorded from foramen ovale (FO) electrodes [51]. Spikes detected visually on FO traces were used to trigger surface EEG averaging and, although there was initially no paroxysmal activity detectable on surface EEG, a low-voltage EEG transient (5–20 μV) was clearly seen to emerge from the noise post averaging. Dipole modelling of this transient consistently permitted the identification of a source located in the mesial temporal structures, close to the FO electrode where the maximal spike had been recorded. These results show that dipole modelling methods can localize the mesiotemporal sources of interictal spikes with an acceptable spatial accuracy.

Such validation studies, however, focus on specific intracranial signals, but epileptologists would prefer to know whether or not dipole models of scalp data can localize the actual generators of interictal spikes. This question can be indirectly addressed by comparing spike modelling data with results from invasive recordings using subdural electrode grids or depth intracerebral electrodes, or with those of anatomical or of interictal functional imaging. In the following three sections, we review data addressing these points.

Dipole sources of interictal spikes versus intracranial recordings

Since the non-invasive presurgical evaluation techniques reflect different pathophysiological aspects in epilepsy, they are not ideal for validating the localization of dipole sources in epileptic paroxysms. Such validation needs to rely upon more direct tools, such as invasive or semi-invasive recordings, but it is necessary to differentiate studies in which scalp and intracranial data

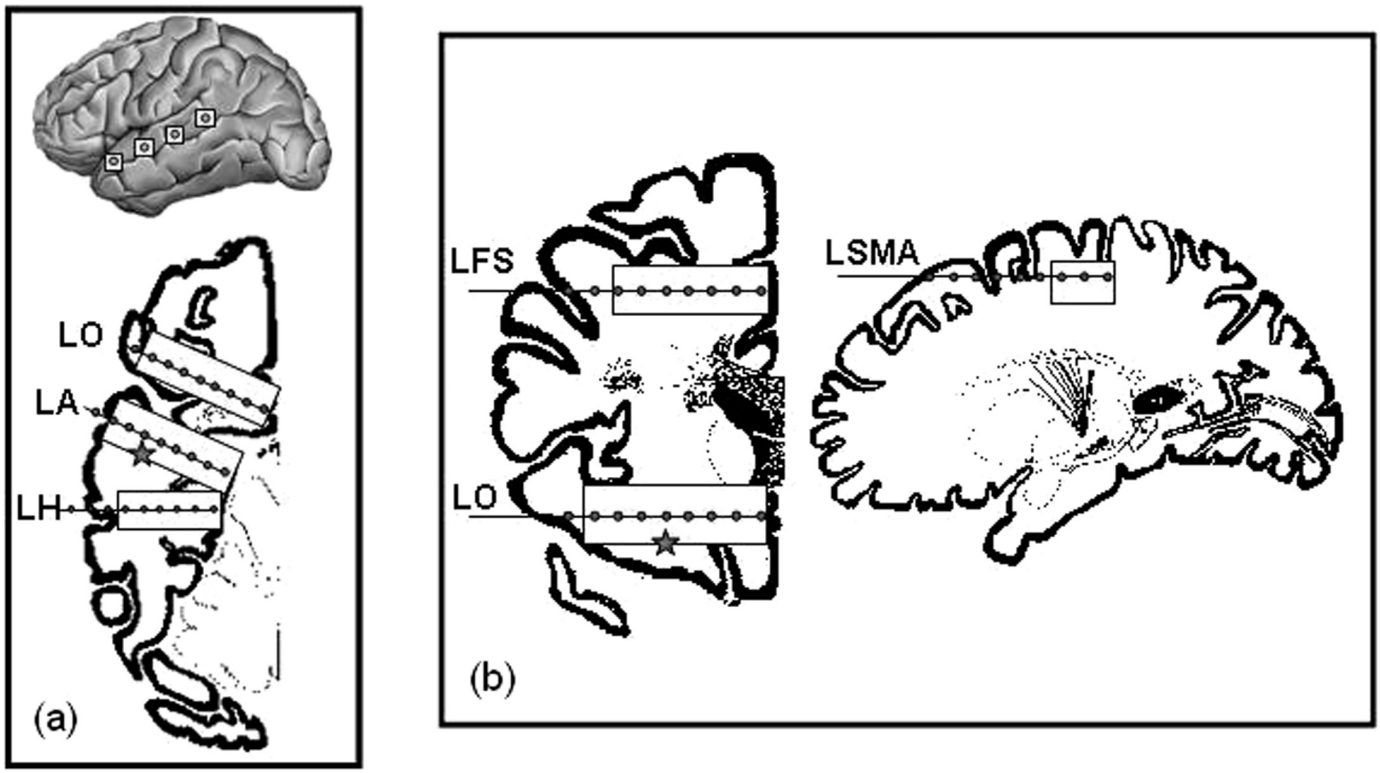


Fig. 66.3 Intracranial correlates of scalp EEG spikes. (a) Scalp spikes were located in the temporal area. (b) Scalp spikes were located in the right frontal area. The figure illustrates the locations of the intracerebral electrode tracks and the position of epidural electrodes in (a). Stars indicate intracerebral contacts in which maximal activity was recorded. Grey rectangles represent the contacts that recorded the spike activity. For example, in (a), contacts 1–8 of the LO electrode, 1–8 of the LA electrode, 1–6 of the LH electrode, as well as the four subdural electrodes on the superior temporal gyrus, are active during the scalp EEG spike. This figure illustrates the fact that generators of a spike restricted to a focal scalp region can be distributed over a large cortical area. LO, left orbitofrontal; LA, left amygdala and anterior middle temporal; LH, left anterior hippocampus and middle temporal gyrus; LSF, left superior frontal; LSMA, left supplementary motor area.

were obtained simultaneously from those obtained otherwise. When EcoG (electrocorticography) or SEEG (stereoelectroencephalography) is not recorded during the scalp EEG session, dipoles are difficult to validate because the risk exists that the scalp and intracranial spikes might not share the same generator.

Several case reports have been published showing a perfect agreement between dipole location and EcoG spikes in lesional cases [52] or in complex cases in which multiple foci are suspected [53,54]. Larger series generally show good concordance between dipole locations and intracranial interictal data. In a group of four patients with focal cortical dysplasia, the localization of MEG spike sources was consistent with interictal intracranial recordings in all cases [55], and Lantz *et al.* showed that, when spike dipoles were spatially stable, their locations were concordant with EcoG recordings [19].

Some studies also demonstrate good concordance between spike dipoles and intracranial ictal onset in mesial temporal lobe epilepsy (TLE) [56,57]. Although some have found that such concordance is higher in TLE than in frontal lobe epilepsy (FLE) [58], spike sources and intracranial ictal data are also reported to have matched in 75% of adults [59] and 90% of children [60] presenting with extratemporal non-lesional epilepsies.

Studies in which simultaneous scalp and intracranial recordings could be achieved are fewer. We have addressed this issue [7,61] to answer the following questions: (1) When a spike is recorded at the surface, what are the spatial characteristics of the underlying activated area? (2) Is the dipole that models a scalp spike located in the region of maximal electric field? (3) When dipole modelling suggests propagation between distinct areas, do intracerebral recordings show spike activity in each of these areas, and are there any intracerebral indices of propagation?

The current finding is that when a spike is recorded at the scalp surface, the intracerebral activity always involves several contacts suggesting the participation of a large cortical area (Fig. 66.3). Conversely, when intracerebral spikes are very focal, either in mesiotemporal structures or even in neocortical regions, no discernible scalp EEG signal is recorded. This result is now widely accepted and was suggested more than 30 years ago from simulated data using a polythene sheet connected to a low-frequency oscillator in an empty skull [62]. These findings have also more recently been confirmed in epileptic patients, in particular by Ebersole's team [57,63,64], using simultaneous EEG and EcoG or SEEG recordings; it is held that a minimal cortical area of 6–8 cm^2 is necessary for a spike to be recorded on scalp EEG. The accuracy of such estimations is, however, limited by the low spatial resolution of intracranial recordings exploring a restricted number of regions. This was confirmed recently by Ray *et al.* [65], who showed that the onset of surface spikes involved between 9 and 15 intracranial electrode contacts. This same study showed that during the rising phase of the surface spike up to the peak, the intracranial generators progressively extended in size. Evaluating the minimal extent of generators leading to a surface spike is thus a challenging issue, since the coverage of intracranial structures is incomplete. Tao *et al.* [66] showed that if 90% of spikes with a source area greater than 10 cm^2 produced scalp EEG potentials, only 10% of spikes with a source surface between 6 and 10 cm^2 and none of those with a source surface <6 cm^2 were detectable on scalp recordings.

A second interesting finding is that in some instances scalp interictal spikes are associated with 'simple' distributions of intracerebral fields (i.e. characterized by a maximum culminating at the time of the surface EEG spikes and by synchronous activity gradually decreasing along the adjacent contacts; see Fig. 66.4a). This does not, however, represent the majority, and in most instances asynchronous activities can be detected in addition to the maximal synchronous peak (Fig. 66.4b) [61]. This complex arrangement of intracerebral fields may be interpreted as reflecting spreading phenomena between regions in which the asynchronous activities are recorded.

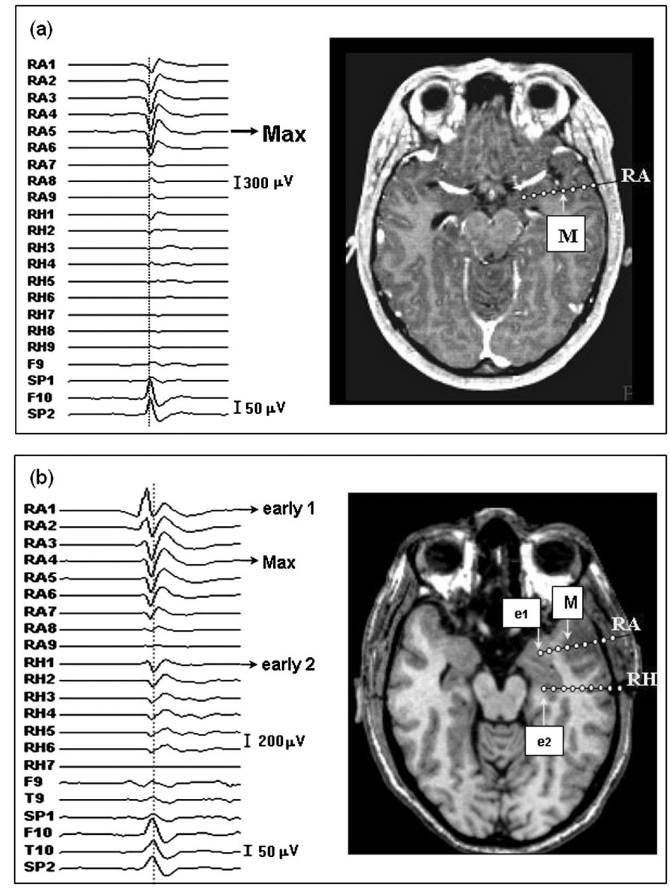


Fig. 66.4 Simple versus complex intracerebral fields associated with surface electroencephalogram (EEG) spikes. (a) Simple spikes. On scalp EEG recordings, the spike is maximal at F10 in the right anterior temporal region. Concomitantly, the maximal intracerebral field is recorded in the right temporal pole (RA5) and gradually decreases along the adjacent intracerebral contacts. No asynchronous activity is recorded elsewhere. (b) Complex spikes. Concomitant with the scalp EEG spike and culminating in the right anterior temporal region (electrode F10), the maximal intracerebral field occurs at the right temporal pole (RA4). Two earlier asynchronous activities can also be detected in the right amygdala (RA1) and hippocampus (RH1). Early intracerebral field(s), e1 and e2. Intracerebral electrodes: contacts 1 are the deepest, and contacts 9 are the most superficial. Scalp electrodes: F9, F10 (anterior low temporal), T9, T10, (middle low temporal) and SP1, SP2 (zygomatic). M, maximal intracerebral field; RA, right amygdala; RH, right anterior hippocampus.

Interestingly, dipole modelling techniques might be able to predict reliably the type of field distribution because, in almost all cases in which intracerebral activity is simple, spikes can be modelled by one source. However, in cases in which intracerebral activity is complex, several dipoles are needed, and when a single model is used, dipoles are usually located at the centre of mass of the intracerebral area activated [67].

Simultaneously combining MEG and EcoG recordings in two patients, Mikuni *et al.* [68] found good concordance when spikes were recorded from the lateral temporal cortex, whereas dipoles were ill-localized when spikes arose from mesiotemporal structures. In our series, no such differences were observed. The main dipole source was located on average 11 mm from the SEEG contact showing the maximal intracerebral potential. In two-thirds of cases good concordance was obtained (1) between main dipole sources and maximal intracerebral fields and (2) between early or late sources and early or late intracerebral fields. In general, they are associated with good temporal concordance, i.e. the delay between the different intracerebral activities was perfectly congruent with the delay between dipole activation curves (Fig. 66.5a). Spatial discordance was found in 16% of cases (Fig. 66.5b), and dipole locations could not be validated in 10% because they were situated in unexplored areas (Fig. 66.5c) [61]. These data confirm that surface EEG spikes are associated with

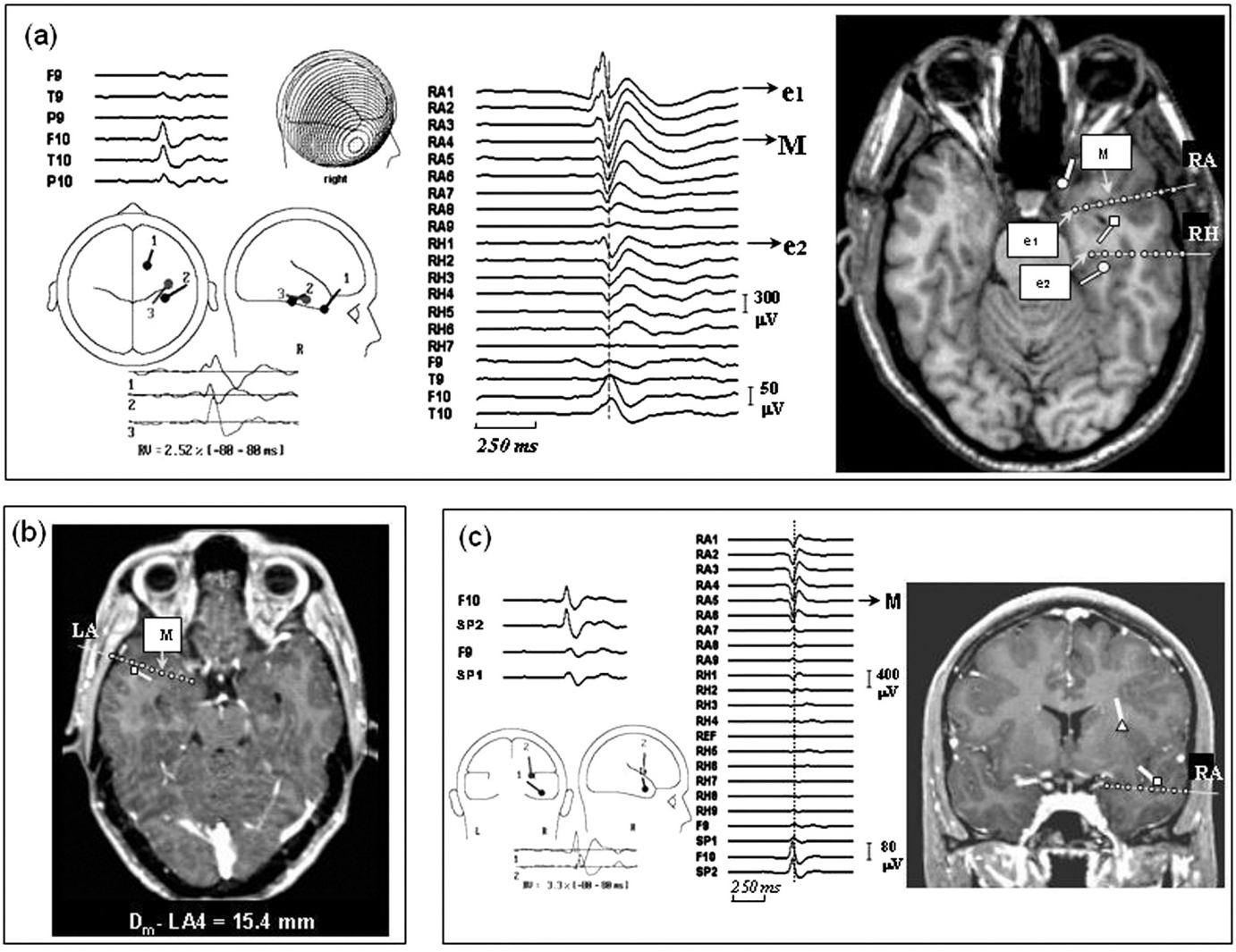


Fig. 66.5 Concordance between spike dipoles and intracerebral fields. (a) Example of spatial and temporal concordance. The two early dipoles (circles) are concordant with the two early intracerebral fields in the amygdala and hippocampus, and the main dipole (square) is concordant with the maximal intracerebral field in the middle temporal gyrus. The dipole activation curves match the sequence of activation observed on intracerebral traces. (b) Example of spatial discordance. The maximal intracerebral field is recorded at LA4 whereas the main source (square) is more lateral and closer to LA6. The distance between the main source and the maximal intracerebral field at LA4 (Dm-LA4) was 15.4 mm. (c) An example of a non-validated source. The late source (triangle) is located in the right insula which was not explored with intracerebral electrodes. In this case the location of this source cannot be confirmed by intracerebral recordings. Early intracerebral fields, e1 and e2. Intracerebral electrodes: contacts 1 are the deepest, and contacts 9 are the most superficial. Scalp electrodes: F9, F10 (anterior low temporal), T9, T10 (middle low temporal), P9, P10 (posterior low temporal) and SP1, SP2 (zygomatic). LA, left amygdala; M, maximal intracerebral field; RA, right amygdala; RH, right anterior hippocampus; circle, early dipoles; square, main dipole; triangle, late dipole.

intracerebral fields distributed over broad cortical areas and rarely occur simultaneously with a focal activity, especially when it is limited to mesiotemporal structures. They imply that modelling the scalp spike by a single source located in the mesial aspect of the temporal lobe may be unreliable.

The aforementioned studies illustrate the difficulties encountered for validating source localization techniques with intracranial data. An essential step towards a better interpretation of source modelling results most likely requires a better understanding of the generation of electrophysiological signals, both from a spatial and from a temporal point of view. We recently made an attempt in that direction by quantitatively investigating the relationship between EEG signals and the spatiotemporal configuration of the underlying neuronal sources [69]. A physiologically plausible model was used to simulate epileptic spikes on scalp EEG and intracerebral EEG signals simultaneously, from a patch of cortex of known location, area and synchronization level. Such a model, in which the ground truth is known, may provide an interesting framework to evaluate source localization methods.

Dipole sources and MRI lesions

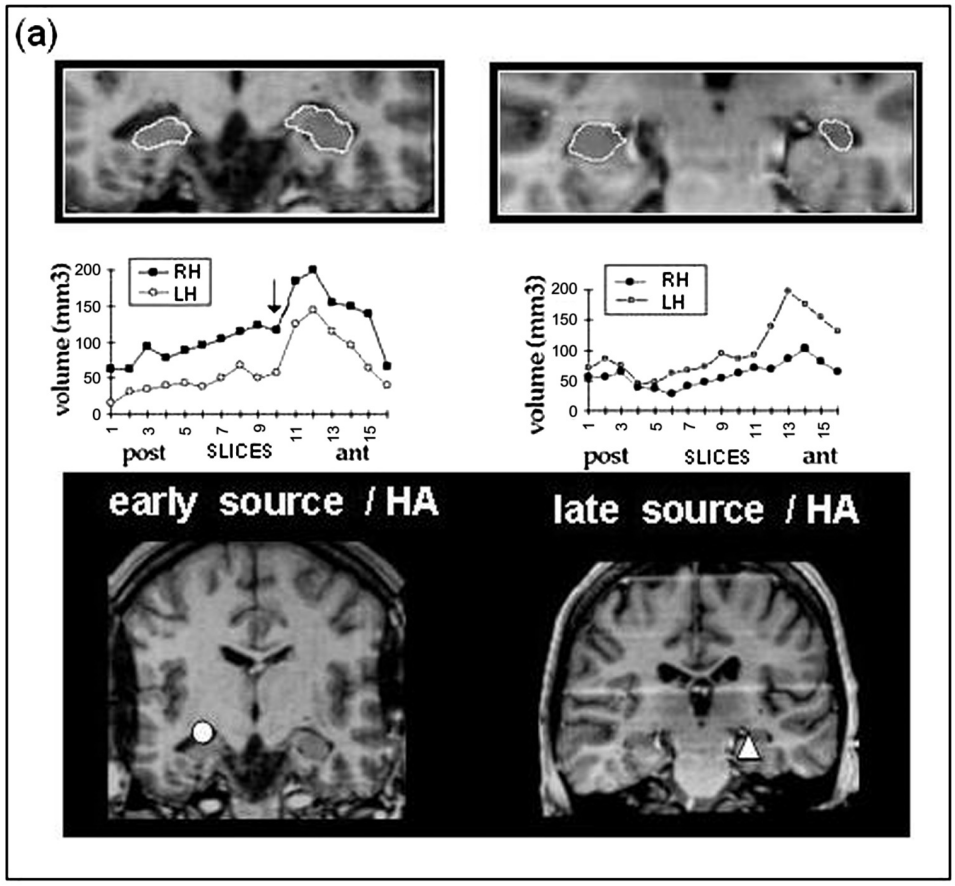
Most studies exploring the relationships between MRI abnormalities and the generators of interictal paroxysms conclude fairly good spatial agreement (summarized in Table 66.2). Most have used spherical head models and single instantaneous dipole fits at the maximum of the interictal spike peak. These results come from a series of various sizes (1–16 patients), including epilepsies of different types, and may therefore be contradictory. However, global analysis shows dipole sources to be located within lesions or within 10 mm in about 80% of cases, regardless of the techniques used to record the spikes (EEG or MEG). Thus, both techniques seem to provide a similar degree of accuracy.

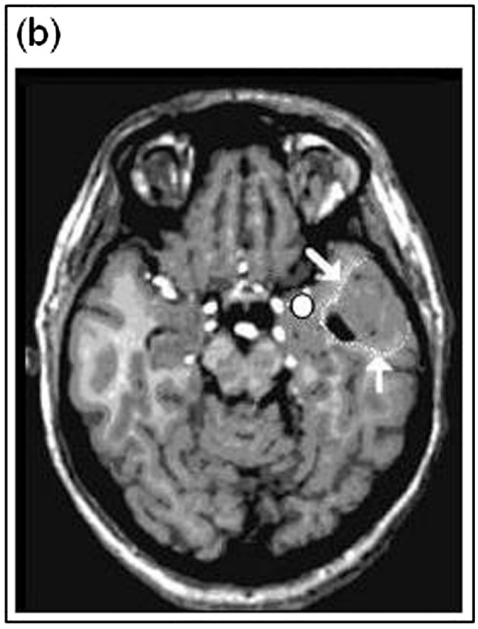
Surprisingly, the concordance between dipole locations and MRI lesion was poorer in some studies using realistic head models (58%) [58,70,71] than in others using spherical head models (79%) but the former are fewer. As far as the type of lesion is concerned, the best agreements between dipole results and lesions are found in focal dysplasia or heterotopia (86%), and next in hippocampal atrophies (79%), whereas a dipole is identified close to tumours in only 50% of cases. Using MEG source imaging, Stephan *et al.* [72] reported that in five out of eight cases of cavernous angiomas interictal spikes sources were located less than 20 mm from the lesion itself or from the surgical scar after unsuccessful lesional resection. They suggested that source modelling could be useful to identify the epileptogenic lesion in patients with multiple cavernous angiomas.

Some authors have studied the spatiotemporal relationships between lesions and the activation sequence of spike sources. From a series of five hippocampal atrophies [73], one frontal gliotic lesion [71] and one frontal dysplasia [74], it has been suggested that sources calculated from the first part of the spike (early and main sources) are more concordant. Our own results obtained from a series of 14 patients [75] are less affirmative. Although in heterotopia or tumour cases the best agreement is obtained for early and main sources (Fig. 66.6b and c), for hippocampal atrophies, dipole sources (indifferently early, main or late) may be located in or outside the atrophic hippocampus, in the temporal and in extratemporal neocortical areas (Fig. 66.6a). In some cases, sources may be located in the hippocampus, even in the absence of any atrophic lesion. Results from space-occupying lesions are very similar (Fig. 66.6b).

Table 66.2 Concordance between the location of spike sources and the location of MRI lesions.

Study	Model and approach	Event	Data	Lesion/dipole concordance (<10 mm)				
				Hippocampal atrophies	Tumours	Focal dysplasia or heterotopia	Other	Total (%)
Stefan *et al.* [73]	Spherical spatiotemporal	Spikes	MEG	5/5	6/8		2/3	81
Nakasato *et al.* [120]	Spherical, Single dipole	Spikes	EEG				1/2	50
			MEG				2/2	100
Knowlton *et al.* [121]	Spherical, single dipole	Spikes	MEG	2/3	2/2	1/1		83
Merlet *et al.* [75]	Spherical, spatiotemporal	Spikes	EEG	7/8	1/1	2/2	2/3	86
Diekmann *et al.* [163]	Spherical, moving dipole	Spikes	EEG		1/4		1/1	40
			MEG		0/4		1/1	20
Krings *et al.* [107]	Spherical, single dipole	Spikes	EEG	2/2	1/1	1/1	4/4	100
		Seizures		3/3	1/1	–	–	100
Shindo *et al.* [58]	Realistic, dipole unique	Spikes	EEG	2/2		0/1	3/4	71
Ossenblok *et al.* [71]	Realistic, spatiotemporal	Spikes	EEG				1/1	100
Scherg *et al.* [74]	Spherical, spatiotemporal	Spikes	EEG			1/1		100
Morioka *et al.* [55]	Spherical, single dipole	Spikes	MEG			3/3		100
Baumgartner *et al.* [164]	Spherical, single dipole	Spikes	MEG				8/8	100
Huppertz *et al.* [70]	Realistic, single dipole	Spikes	EEG	1/4	0/1		4/6	45
		Delta		0/2	1/1		5/6	67
Total	Spherical	Spikes	EEG	9/10	3/6	4/4	8/10	79.3
			MEG	7/8	8/14	3/3	13/14	79.4
	Realistic	Spikes	(EEG)	3/6	0/1	0/1	8/11	57.8
Total (% of concordance)				**79%**	**52%**	**87%**	**83%**	





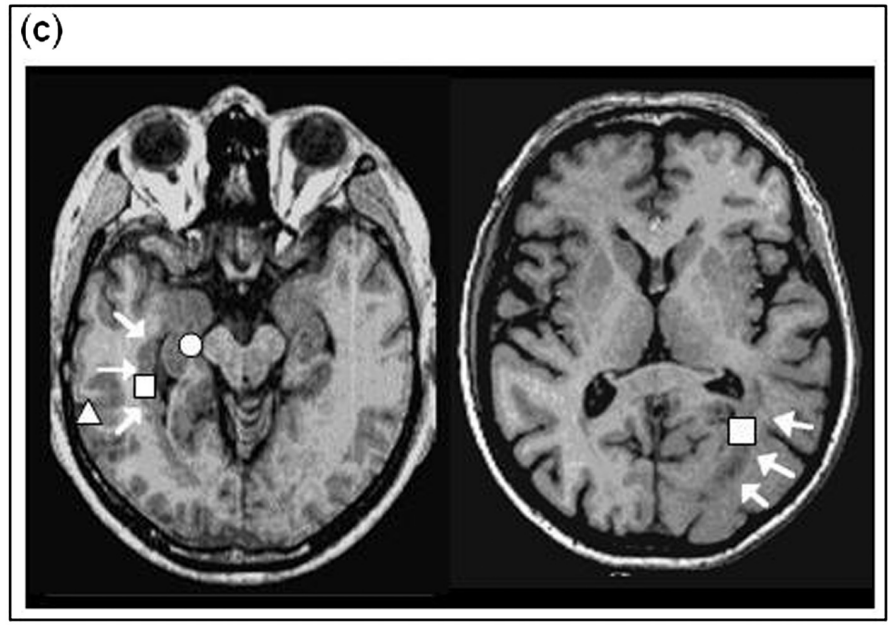


Fig. 66.6 Spike dipoles and MRI lesions. (a) Hippocampal atrophy. Two examples are given. The curves represent the volumes of the right hippocampus (RH) and the left hippocampus (LH) measured on coronal slices between the anterior (ant) and posterior (post) aspects of the hippocampus. The top of the figure illustrates diffuse LH atrophy (on the left), and also atrophy of the anterior aspect of the hippocampus (on the right). In both cases at least one source was located in the atrophic hippocampus, but this source was the early one in the first case (white circle) and the late one in the second case (white triangle). (b) A tumour. In this patient, the early source of interictal spikes is located in the vicinity of a grade III xanthoastrocytoma (arrows and dotted line). (c) Grey matter heterotopia. In these two patients (left: left temporal periventricular heterotopia; right: right occipital heterotopia) the main sources (white squares) of interictal spikes were localized to within the abnormal grey matter in both cases. In the patient with periventricular heterotopia (left), the dipole modelling results suggest that spikes originate from the hippocampus and spread within the lesion, whereas in the other patient (right), they originate from the lesion without involving other regions.

Considering these data, the spatial relationships between lesions and the localization of interictal spikes can vary and seem to depend on the lesion type. In the majority of cases, an overlap exists between the lesional zone and the network involved during interictal spikes, but when timing is considered, dipole results may suggest either origin or propagation within the lesion. Obviously the relationships are complex and echo the relations between electrophysiological and structural abnormalities [76–78].

Dipole sources of interictal spikes and metabolic abnormalities

Most [^{18}F]fluorodeoxyglucose (FDG) PET studies show interictal hypometabolism in 60–80% of partial epilepsies (see ref. 79 for a review). However, the relation between epileptogenesis and glucose hypometabolism is not straightforward. For instance, it appears that the ability of perilesional cortex to generate seizures bears no relation to the presence of perilesional glucose hypometabolism in focal lesions such as cavernous angiomas [80].

Whilst comparing, in the same group of TLE patients, the location of interictal spike sources with that of the FDG-PET hypometabolic zone [81], we found that when spikes are modelled by unilateral temporal sources, the latter were located within the hypometabolic zone. However, glucose hypometabolism was not significantly more pronounced in regions where dipoles were localized. Conversely, in a majority of patients in whom late extratemporal involvement was suggested by interictal spike modelling, hypometabolism was restricted to mesiotemporal areas. In FLE, the spatial relationships between glucose hypometabolism and spike source can be extremely diverse. Dipole sources can be located either within the hypometabolic area when several lobes are involved, or outside the hypometabolic zone in cases in which the metabolic abnormality is very focal.

The above findings are in agreement with those reported by Lantz *et al.* [19] describing the relations between the focal interictal decreases in cerebral blood flow (CBF) on SPECT images, and the localization of spike sources. They found a better concordance between the low CBF zone and sources of interictal spikes when dipoles were localized within one temporal lobe. These results have been corroborated by two similar studies showing a good concordance between FDG-PET abnormalities and dipole sources in both interictal MEG [82] and EEG [83] spikes, when these were unilateral temporal. As with our group of patients, these authors failed to find a correlation between the degree of decrease in glucose uptake and dipole location. They also found less agreement between PET and dipoles when extratemporal involvement was suggested by interictal spike modelling.

Taken together, the above studies converge on the conclusion that, when spike sources are localized to one temporal lobe, FDG images tend to confirm the dipole locations; this could suggest some functional link between the metabolic dysfunction and the processes responsible for spikes. Conversely, when spikes are spread outside the temporal lobe or a frontal origin is suggested by dipole modelling, the metabolic and electrophysiological processes seem partly independent.

Interpretation of dipole modelling of interictal spikes: the concept of 'interictal network'

Are interictal spikes 'simple' or 'distributed' phenomena?

When dipole modelling methods are applied to interictal spikes, several source distributions may be obtained. In rare instances, interictal spikes can be adequately modelled by a single dipole. For example, Fig. 66.2a shows that spikes from a patient with parieto-occipital epilepsy could be modelled by a single source within an occipital grey matter heterotopia. In the majority of cases, however, several dipoles are required. These sources are usually located in distinct anatomical regions, and are activated sequentially but overlap in time, as illustrated in Fig. 66.2b. Such patterns lead to the concept of 'spreading' activity and distributed sources during a single spike. It is historically noteworthy that most of the teams involved in spike dipole modelling have gradually been moving from 'unique source' [84–86] to 'multiple source' activation or volumetric models of interictal paroxysms [87–90].

The interictal network in temporal lobe epilepsy

Modelling spikes in temporal lobe epilepsy (TLE) is helpful to address whether or not mesial, lateral or both temporal cortices are involved in spike generation. In general, the majority of spikes culminating at temporal electrodes can be modelled by dipoles localized to the ipsilateral temporal lobe. However, within this group it is possible to distinguish between 'early mesial' and 'early neocortical' involvement, depending on whether or not early sources localize to mesial or lateral temporal structures. Early mesial involvement seems to be more frequently observed, suggesting that mesiotemporal structures function as a trigger in the interictal network [3,56,81,90–92]. However, the opposite may also be observed and suggests that mesiotemporal structures can also work as a secondary relay in this process [73,81,89].

Whatever the model of sequential activation, interictal spikes appear as distributed phenomena that involve both mesial and neocortical temporal regions, supporting the hypothesis that sustained reciprocal interactions between mesial and neocortical structures exist during interictal temporal spikes. Because of the intrinsic properties of the mesiotemporal regions, particularly the hippocampus, which appears essential to maintaining temporal discharges, results from spike source modelling support the hypothesis that these structures act not only as initial triggers, but also as secondary 'pacemakers' contributing to the amplification, prolongation and spread of ictal discharges.

In certain patients, in addition to the activation of mesial and neocortical temporal regions, it is possible to identify late involvement of extratemporal structures. For example, using dipole modelling techniques, Lantz *et al.* [19] described the combined activation of temporal and orbitofrontal regions during spikes culminating at the temporal scalp electrodes.

In our experience, the most frequently involved extratemporal regions are orbitofrontal, inferior parietal, insular and central opercular regions. Their involvement during ictal propagation is not really surprising, but the fact that they can be recruited during a rapid temporal interictal paroxysm is somewhat more so. Nevertheless, such data are confirmed by electrocorticographic mea-

surements in which the interictal spikes of TLE may be multifocal, often covering a large area of the temporal lobe, and may involve adjacent extratemporal structures such as the inferior parietal lobule or the orbitofrontal cortex [93]. These results favour activation of a distributed network during interictal paroxysms, which not only involves mesial and lateral aspects of temporal lobe but sometimes exceeds temporal lobe limits.

The interictal network in frontal lobe epilepsy

There have been few reports of dipole modelling results in FLE. In general, frontal spikes are recognized as more complex than temporal spikes. They are characterized by a more diverse range of topographies for a given patient (greater number of different types of spikes), requiring more sources to model, and wider spatial extents suggesting interlobar and interhemispheric propagation.

Ito *et al.* [94], correlating the locations of frontal spike dipole sources with ictal semiology, showed frequent orbitofrontal involvement, rapid bilateral involvement and, in some instances, propagation to extrafrontal regions. Accordingly, studies using frequency analysis, in particular coherence and phase measurements [95,96] during bilaterally synchronous spike–wave activity, reported high coherence values between homologous EEG channels on both hemispheres, which favour direct interfrontal connections potentially through the corpus callosum or anterior commissure.

Finally, using principal component analysis (PCA) in a group of 39 children, Rodin *et al.* [97] showed a greater complexity of frontal interictal spikes, compared with temporal and occipital ones. These results are in favour of a caudorostral gradient of complexity reflecting recruitment within the interictal network of an increasing number of structures, as anterior regions are involved in the spiking process. In practice, the high complexity of frontal interictal spikes together with the multifocal distributions of their dipolar sources does cast some doubt on the reliability of such models, in the context of FLE [98].

Dipole modelling of ictal discharges

Studies assessing the spatial relationship between interictal and ictal events give extremely variable results. The concordance between regions generating interictal and ictal paroxysms is generally good depending on the type of epilepsy, the localizing method and its accuracy. In the case of hemispherical lateralization, excellent agreement between interictal and ictal events is observed in partial mono-focal epilepsies, even perfect agreement in certain series [99]. In the case of lobar localization, concordance remains good, especially for TLEs [100,101], but in the case of sublobar localization concordance drops [102]. Using combined scalp and invasive EEGs, Marks *et al.* [103] showed that interictal spikes and ictal discharges originate from the same area in only 58% of TLEs. By means of intracerebral recordings, Rougier estimated that the zones from which interictal spikes and seizures arose were similar in 55% of patients suffering from TLE, but in only 30% of patients suffering from frontal seizures [104].

Seizure modelling is more complex than interictal spike modelling owing to a low signal–noise ratio, the presence of artefacts and the spread of activity which may be extensive and entail rapid changes in the complex source configurations over time. Some authors have demonstrated the feasibility of ictal dipole models [90,105] with good agreement sometimes in the locations of interictal and ictal events [19,56,106,107]. Other studies indicate low yield (30–40% of patients) when dipole modelling is applied directly to ictal signals [7,108].

Interestingly, in cases in which dipole models fail, the intracranial field correlates of the first scalp EEG change are bilateral and maximal in the mesiotemporal regions. This suggests that bilateral involvement at seizure onset may lead to dipoles located at the centre of the head or reaching different locations when initial conditions change. In case reports of one and two patients [109,110], good agreement was also found between the dipole sources of ictal events and ictal onsets as defined on non-simultaneous EcoG recordings.

During simultaneous recordings, ictal dipole sources are usually concordant with ictal onset, provided the latter does not occur in mesiotemporal regions [7]. When maximal activity is located within mesiotemporal structures, dipoles are usually displaced more laterally. Comparisons between ictal dipoles and ictal intracerebral fields are hampered when ictal onsets occur very focally, so that no scalp EEG activity can be simultaneously detected. Finally, additional sources are often found scattered in diverse cortical regions so that, in a majority, their significance cannot be established. It is possible, for example, that, apart from noise, these additional sources reflect spreading to regions beyond the primary epileptic zone.

Clinical relevance of dipole modelling results

Does spike source modelling corroborate epilepsy surgery findings?

This issue has been recently reviewed by Plummer *et al.* [111]. Few studies have examined sensitivity of spike source modelling for localizing the epileptogenic zone and most have compared the location of dipoles with resection margins in good-outcome patients (Engel class I and II). When dipole modelling was performed on ictal signals, concordance rates between ictal sources and resection margins were very poor (only 10% of cases) [108], but concordance was higher for interictal spike sources. Comparing source models of interictal MEG spikes, MRI, interictal/ictal video-EEG and interictal/ictal intracerebral recordings, some found dipole modelling to be the second most sensitive method (57% concordance) for predicting the epileptogenic zone after ictal intracerebral recordings (62%) in TLE [112]. In extratemporal cases this dropped to 44% versus 81% for ictal intracerebral recordings. In another study, sensitivity reached 94% [113]; however, this result is not very conclusive because good concordance between spike dipoles and resection localization was also found in 85% of patients with bad surgical outcome (Engel class III and IV). A recent study by Michel *et al.* [32] using single-source dipolar distributed modelling of 128-channel EEG data reported that in 18 out of 24 patients who underwent epilepsy surgery (17 temporal, seven extratemporal), all but two with lesional focal epilepsy, the source maximum fell within the border of the resection area; 16 of these patients had an Engel class I outcome. However the investigators were not blinded to MRI data during

the source-fitting procedure. In a surgical paediatric study by Sperli *et al.* [114], the authors quantified the concordance between the resected volume and the extent of the statistically thresholded distributed sources solution [114]. A satisfying concordance (>50% overlap) was observed in 27 out of 30 patients, most of them being seizure free after surgery.

The only study that has addressed directly the question of whether or not the spatial extent of the spiking network (as defined by spike modelling) may help in delineating the epileptogenic zone and planning resection is the MEG study by Fischer *et al.* [24] in which a single equivalent dipole model was used in a series of 33 patients who underwent epilepsy surgery. They showed that the concentration of spike sources in a restricted area and a high coverage of this area by the resection volume correlate with a good outcome. In multiple spatiotemporal dipole models, the fact that a single spike may reflect the activation of several sources does not imply that all of them need to be removed to control seizures, and, conversely, seizure spread may include areas uninvolved in interictal spiking. It is likely, for instance, that a number of TLEs remedied by mesial temporal surgery may actually have shown interictal spike sources in the lateral neocortex prior to surgery, and this remains to be demonstrated through a dedicated prospective study.

Does spike source modelling help to lateralize the focus in TLE with bilateral interictal spikes?

In some cases of independent bilateral temporal spiking, early sources for both can be localized to the same side (Fig. 66.7). In our experience, this also corresponds to the side of most frequent spiking, and this is clinically relevant since hemispheric predominance is observed in 80% of TLEs with bilaterally asynchronous spiking [115–117]. The laterality is well correlated with the side from which the seizures originate [99,117] and is associated with better surgical outcome when operating on the same side [118].

Is congruence between spike source modelling and other investigations a reliable predictor of surgery outcome?

The clinical relevance of spike modelling cannot be evaluated without examining concordance between source locations and structural (MRI) or functional neuroimaging data. Stefan *et al.* [119] reported surgical success when dipole sources of MEG spikes were spatially congruent with PET, SPECT and interictal EcoG results. Lamusuo *et al.* [82] have also reported good outcomes in patients in whom dipole modelling results agreed with PET data, whereas the others were not cured by surgery. A good agreement between dipole locations and MRI lesions has likewise been widely reported to predict good surgical outcome [55,107,120,121]. Similarly, Smith *et al.* [59] found concordance between EcoG results and the localization of MEG interictal spikes in 75% of patients, amongst whom surgical results were good in 61%; surgery failed in all discordant cases.

Is source modelling of ictal signals clinically useful?

The largest prospective study of scalp ictal dipole modelling hitherto available is that of Boon *et al.* [122], which evaluated the contribution to the clinical decision making in 100 cases of refractory partial epilepsy, which was mostly lesional (83%). Ictal data were obtained in 93 patients, of whom 62 could not undergo source modelling of ictal events owing to artefact contamination. In 14 out of the 31 remaining patients source localization was considered as clinically useful, mostly by showing spatial incongruence between lesional and ictal EEG abnormalities (10 patients). This study suffers from some methodological deficiencies detailed in the review by Plummer *et al.* [111]; in particular, modelling was limited to the use of a single regional dipole and results were categorized as either vertical (type 1) or radial (type 2) dipoles, according to the early classification first proposed by Ebersole and Wade [123] in which type 1 and type 2 dipoles were considered as equivalent to mesiobasal and lateral temporal sources, respectively. This classification is now viewed as an oversimplification by Ebersole himself [124]. Nevertheless, this study

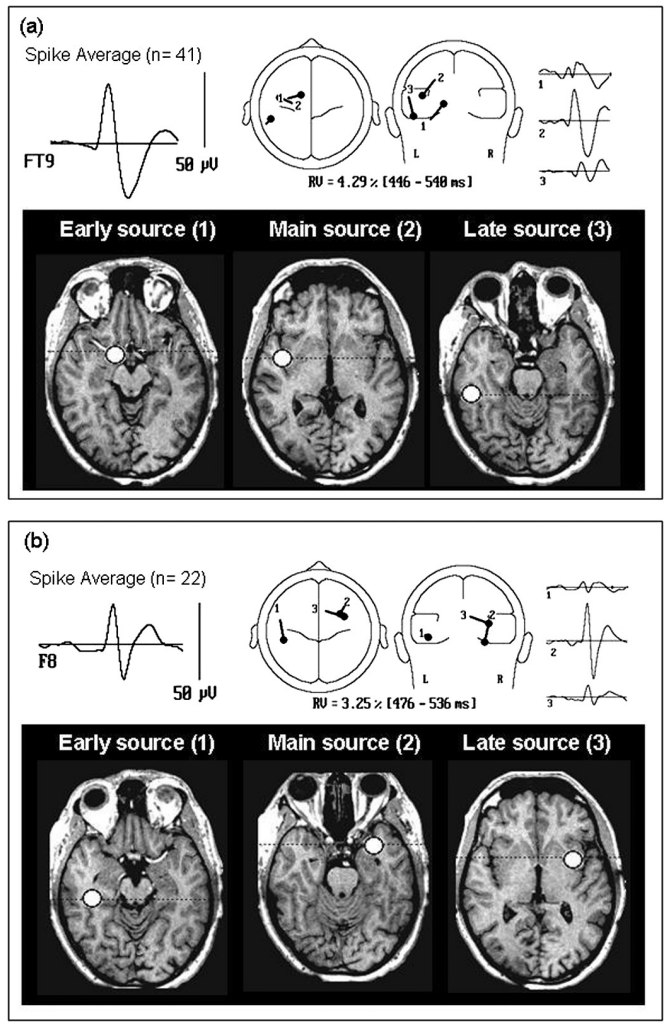


Fig. 66.7 Dipole modelling of bitemporal interictal spikes in TLE**.** In this example, independent bilateral temporal spikes could be averaged. (a) The left-sided (FT9) spikes were the most frequent and could be modelled by three left temporal dipoles, suggesting spread from mesial to lateral temporal regions. (b) The right-sided (F8) spikes were less frequent but had an early source still located in the left mesiotemporal region, as for FT9 spikes. Dipole modelling here suggests spreading from the left mesiotemporal region to the right temporal pole, and later the right insula.

presents the advantage of showing that ictal dipole modelling is a hazardous procedure that has been feasible in less than one-third of patients.

EEG-correlated functional MRI in epilepsy

Functional magnetic resonance imaging has proved over the years to be a powerful non-invasive tool to identify the components of a brain network involved in a sensorimotor or cognitive process, in which the experimental condition differs from the control condition in a way that is controlled by the experimenter [125]. In epilepsy, fMRI has thus been evaluated as an alternative to invasive investigations for localizing language or memory functions. In this chapter, we will exclusively review the applications of EEG-correlated fMRI (EEG/fMRI), with the 'control' condition being that in which the EEG is at baseline and the 'experimental' condition being that in which the EEG shows interictal paroxysmal activity or epileptic discharges.

It is well established that electrophysiological techniques such as EEG and MEG have higher temporal resolution than metabolic- or haemodynamic-based imaging techniques such as fMRI. The millisecond-scale changes of neuronal activity related to seizures or interictal spikes can be tracked online using EEG/MEG. Conversely, as discussed earlier in this chapter in the section 'Methodological aspects', the major drawbacks of those methods is the difficulty in modelling the spatial sources of surface-recorded events. It is therefore generally assumed that the spatial resolution of EEG and MEG modelling is less than that of fMRI. These considerations highlight the theoretically complementary benefits of combining these two approaches to map brain neural events [126,127].

Using fMRI alone, Jackson *et al.* [128] first described concordant areas of activation, based on the visual inspection of subtraction images, in partial motor seizures. Other reports [129–131] have since described concordant fMRI-detectable activation in relation to either assumed seizure activity or overt clinical seizures, but with ever-present risks of motion-related artefact. Using continuous EEG-correlated fMRI, Salek-Haddadi *et al.* [132] were the first to be able to capture a focal subclinical electrographic seizure in its entirety. They reported a cluster of activation concordant with the EEG focus followed by a deep and prolonged undershoot in keeping with ictal physiology data from several other techniques. Although most of the early studies of EEG-correlated fMRI were mainly focused on methodological difficulties, clinical studies have recently flourished (see ref. 133 for a review).

Over the years, the status of EEG/fMRI investigations has progressively changed. With hardware and signal processing improvements, the clinical recording of EEGs inside the MRI scanner is now feasible, and the number of published studies on that topic is increasing rapidly. Some recent studies suggest that it might provide new information for patients being considered for surgery and some clues to understand the neurobiology of epilepsy. Still, the complex pattern of individual signal change for a particular patient is not fully understood and large prospective studies are still lacking for the confirmation of definite use. From a clinical point of view, large prospective studies using EEG/fMRI as a presurgical tool are needed to evaluate whether or not the technique contributes to seizure relief in those patients.

Physiological origin of functional MRI signal

An increase is neural activity is accompanied by an increase in the cerebral rate of oxygen consumption ($CMRO_2$) and a much larger increase in local cerebral blood flow [134]. Owing to this imbalance, local capillary and venous blood are more oxygenated. The magnetic changes associated with the concomitant decrease in local deoxygenated haemoglobin are the basis for the fMRI blood oxygen level-dependent (BOLD) signal [135,136]. Therefore, the complex interplay between blood flow, blood volume and oxygen consumption resulting from the neurovascular coupling is at the origin of the BOLD signal in fMRI studies. The neural activity that gives rise to fMRI BOLD signal is not fully understood, but recent animal studies have shown that 'local field power', as an index of postsynaptic membrane oscillations (and hence local synaptic activity), correlates in time with the BOLD response [137], whereas action potentials, and thus neuronal spiking, are less correlated with BOLD signal. Moreover, dynamic changes in neural synchronization are also possibly involved in the genesis of the BOLD signal [138].

Under a magnetic field strength of 4 tesla (T), it has been shown that BOLD signal is largely dependent on venous contributions [139]. In other words, BOLD changes can reflect a downstream effect, thus reducing spatial resolution of fMRI for the mapping of the underlying neuronal activity [140].

Finally, the sensitivity of fMRI to detect BOLD signal changes related to epileptic activity is not the same across brain regions as a result of non-homogeneous magnetic fields at tissue boundaries. This can be manifest in the orbitofrontal cortex or basal portions of the temporal lobe, in which signal loss may be particularly high [141].

Methodological questions

Is it safe for the patient?

Although rapidly changing magnetic fields inducing a current that might theoretically induce heat from electrodes, safe recordings can be obtained by using non-ferrous electrodes and leads and avoiding current loops involving the patient. Over the years, the recording of EEG during fMRI has proved to be safe for the patient and no incident has been reported to date.

What is the quality of EEG?

The quality of EEG within the MRI scanner is reduced compared with that of the EEG outside, even within a static magnetic field. Immobilization of the head and wires reduces artefacts caused by electrode movements. During scanning, many sources of artefacts are known. Artefacts related to gradient switching have high amplitudes compared with EEG signal, such that EEG is unrecognizable during frame acquisition (Fig. 66.8). This can be avoided by scanning only after the observation of spikes, and it imposes constraints on the paradigm used. This procedure is largely abandoned today. Gradient switching-related

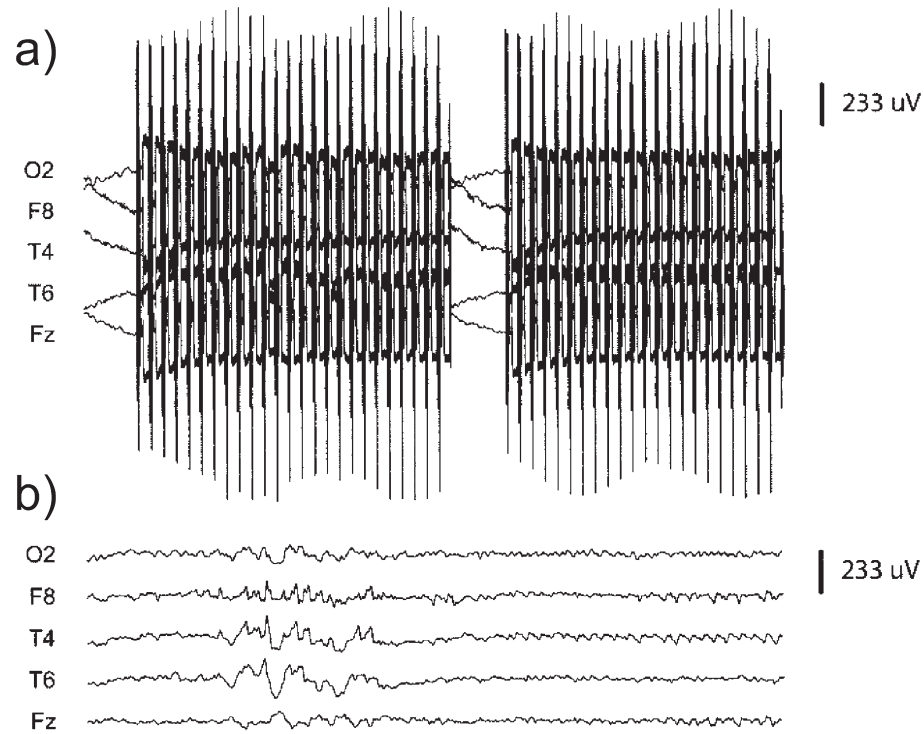


Fig. 66.8 Postprocessing of electroencephalogram (EEG) artefacts during EEG functional MRI (fMRI) acquisitions. (a) EEG trace during scanning. EEG paroxysms are not identifiable because of the switching of the magnetic resonance gradients which induce very large artefacts on the EEG. (b) Artefact removal (subtraction of an average artefact waveform). EEG paroxysms are now visible and enable event-related fMRI analysis. Adapted with permission from ref. 133.

artefacts can be modelled as a linear and time-invariant system. The most widely used method to remove the gradient artefact consists of estimating the artefact and subtracting it from each frame, followed by adaptive noise cancellation [142]. Other methods take advantage of the frequency structure of the artefact [143]. Modern postprocessing techniques permit the identification of epileptiform discharges after gradient artefact removal. Lastly, pulse (or ballistocardiogram) artefacts produced by heartbeats can be removed either by averaging and subtraction [142] or by filtering [144] or independent component analysis [145].

Which is the optimal paradigm of acquisition?

In the early years, the most common paradigm was interleaved acquisition. The acquisition was either aperiodic and triggered by spikes detected during the session [146] or periodic (with a sufficiently long duty cycle to allow for EEG interpretation in between imaging). During the last 5 years, advances in signal processing using the automatic removal of artefacts have enabled the continuous recording of electroencephalography during the session, which is therefore the most common mode of acquisition [127]. These techniques may be used offline but also online, with a direct high-quality visualization of EEG. One advantage of continuous acquisition is that the haemodynamic response function can be calculated, thus permitting a more accurate description of neural events underlying EEG events in the time domain [147].

Which are the principles of statistical analysis?

Despite the well-known high spatial resolution of fMRI, one has to keep in mind that images produced by fMRI depend on modelization of BOLD signal responses related to neural events. In event-related fMRI, the statistical methods most widely used are those developed by Friston *et al.* [148]. In this approach, the signal at each voxel of the brain is statistically compared with a model constructed by convolving impulses corresponding to the timing of the spikes (the events) with one or more basic functions, representing the haemodynamic response function (HRF). A statistical map is constructed and represents the proximity between the model and the data, and therefore the probability that a given region will be activated. One critical step of this approach is therefore to select a valid model, represented here by the HRF. In classical fMRI recordings, it is assumed that the time-course of the HRF to interictal epileptic discharges matches that of the response to brief physiological stimuli with a peak at approximately 2–6 s after onset. This 'canonical' HRF model is widely used but its validity for epileptic events is not definitively established. For example, the HRF associated with a single spike may last 10 to 15 seconds, which may be problematic for temporally overlapping bursts of spikes [149]. Moreover, when measured in epileptic patients, the HRF may exhibit some inter- and even intraindividual variability [149,150], and it was found very recently that responses with shapes that are different from the canonical response may occur at a distance from the suspected generator of epileptic activity, either being a false-positive finding or potentially reflecting propagation effects [151].

Lastly, the constructed map is statistically thresholded so that only voxels above a certain threshold are presumed to be involved in spike generation. Various approaches have been proposed, either parametric or non-parametric, impacting the clinical interpretation of the data.

What is the signification of increased and decreased blood oxygen level-dependent signal?

In EEG/fMRI studies, it is generally considered that the interictal spiking results in a higher level of neuronal activity, and thus an increase in the BOLD signal (so-called *activation*). Increases in postsynaptic activity, whether excitatory or inhibitory, result in an increase in oxidative metabolism and eventually in an increase in the BOLD signal. However, spikes may induce not only BOLD increases but also BOLD decreases (so-called *deactivation*). A BOLD signal decrease can be observed remotely and, more surprisingly, near or within the spiking area. The significance of such deactivations is still unresolved. Deactivation can reflect (1) a decrease in synaptic activity; (2) a GABAergic mediated inhibition resulting in a reduced neuronal firing at low energetic cost; (3) an abnormal vascular coupling or (4) vascular steal in regions surrounding activated areas. While some deactivations are clearly lying in the spiking zone and specific of spike genesis, some others are not directly linked to the epileptogenic process itself. These deactivations can reflect a disruption of ongoing activity in regions that are active in the resting state such as posterior precuneus and frontal mesial cortex. Whether activity changes related to interictal spiking in these so-called 'default mode' brain regions participate in interictal cognitive disturbances is an open and exciting issue.

Clinical studies: EEG/fMRI as a clinical tool

Yield of spike-correlated blood oxygen level-dependent signal changes

In most studies, patients are preselected on the presence of a high rate of interictal spiking. Few systematic studies with large cohorts have evaluated the detection rate of the EEG/fMRI technique. In this case, detection rate is defined as the ratio between the total number of significant spike-related BOLD increases (activation) or decreases (deactivation) and the number of spike groups simultaneously recorded during the study.

Globally, the detection rate of spike-correlated BOLD change varies between 40% and 60% among patients with focal epileptic paroxysms according to studies in adult case series. In the study by Al-Asmi *et al.* [152] involving 38 patients, 39% of the fMRI acquisitions showed spike-correlated BOLD activation. Bagshaw *et al.* [150] showed in a group of 21 patients that the detection yield increased from 45% to 62.5% when using patient-specific HRF. Salek-Haddadi *et al.* [153] reported in a focal epilepsy group that significant haemodynamic correlates were found in 68% of the patients with spikes. Bonaventura *et al.* [154], in a cohort of 43 patients, reported that 49% of the studies showed significant BOLD changes. More recently, Zijlmans *et al.* [155] found a significant BOLD response in 57% of a group of 64 patients. The highest yield of spike-correlated BOLD signal changes (92%) was reported in a recent paediatric cohort that included 37 children; this could possibly be explained by their use of patient-specific HRF and by a high spiking rate in these children [156].

The detection yield of spike-correlated BOLD signal changes also depends on patient characteristics. Thus, the likelihood of a significant response seems to be dependent on the spike rate during the session, but also on spike morphology and temporal distribution of spiking, bursts of spikes being more likely to generate significant results than isolated single spikes [153]. The yield of EEG/fMRI studies in generalized epilepsy is generally higher, for example Aghakhani *et al.* [157] reported significant BOLD changes in 14 out of 15 patients during generalized spike–wave discharges.

Interictal network identification and EEG/fMRI

In the absence of any gold standard it is difficult to assess the reliability of BOLD changes localization to map the area producing interictal spiking. Few studies have compared the spatial distribution of BOLD changes with invasive intracranial data. The largest study investigating the concordance between EEG/fMRI signal and stereotactic EEG comprised only five patients and showed that, if intracranial EEG was sampled from near (within 20–40 mm) a region of BOLD changes, at least one contact presented spikes [158]. However, fMRI was blind to some interictal spiking areas identified by depth recordings, particularly in the basal temporal regions. Interestingly, both activation and deactivation had a localizing value. Moreover, the presence of low-frequency abnormalities such as slow wave was associated more with BOLD activation than with deactivation. Clearly, more studies are needed to confirm the validity of those results in a large cohort with different pathological conditions.

EEG/fMRI and epileptogenic zone mapping

More recent studies have evaluated whether or not EEG/fMRI is a valuable tool to determine the epileptogenic zone, which can be distinct from, or overlapping with, the spiking area. Salek-Haddadi *et al.* [153] brought encouraging results by showing that significant haemodynamic changes on fMRI were highly, but not entirely, concordant with the presumed site(s) of seizure generation (Fig. 66.9). Still, no direct validation by surgical procedure

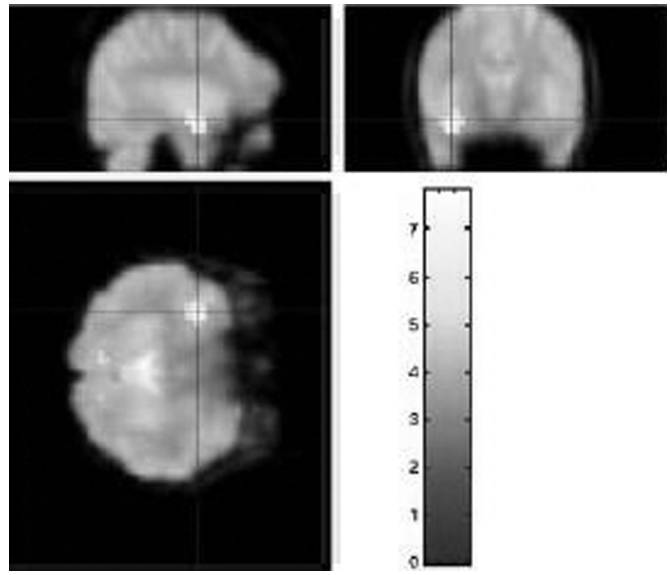


Fig. 66.9 Example of electroencephalogram/functional MRI (EEG/fMRI) study in a patient suffering from left temporal lobe epilepsy. Structural MRI showed left hippocampal sclerosis and scalp EEG revealed left temporal spikes in this patient. EEG/fMRI revealed a highly concordant cluster of temporal lobe activation (local BOLD increase in white pixels). Adapted with permission from ref. 153.

and follow-up is provided in that study. In the study from Bonaventura *et al.* [154], in which focal spike-correlated BOLD changes were seen in 18 out of 21 patients, the haemodynamic foci were congruent with electroclinical data.

Because new physiological tools are mostly needed for complex cases, Ziljmans *et al.* [155] evaluated EEG/fMRI in a cohort of patients rejected for epilepsy surgery because of non-conclusive presurgical seizure onset zone determination. In that difficult group, 8 out of 29 patients presented significant BOLD changes. In four patients, EEG/fMRI brought new localization information, leading to confirmative EEG intracranial recordings and improved localization in four out of six unclear foci. Lastly, in patients with presumed multifocality, EEG/fMRI identified one single focus in one patient and confirmed multifocality in four out of five patients.

Spike-related BOLD changes in different pathologies

During the last years, efforts have been made towards understanding the mechanisms of epileptogenicity of different types of lesions using EEG/fMRI. These studies focused mostly on malformations of cortical development. One study comprised five subjects with focal cortical dysplasia and one with a ganglioma [159], and another study included nine patients with polymicrogyria [160]. Signal changes were found in lesional, near-lesional or possibly subcortical areas, with no specific pattern. The authors speculated that regions exhibiting BOLD variations distant from epileptogenic foci have abnormal functional connections with the lesion area or are parts of the cortical–subcortical circuits involved in the genesis or spread of interictal discharges. Similar findings were found in an EEG/fMRI study of 14 patients with grey matter heterotopia, which showed BOLD activations and deactivations occurring within, near or distant from the lesion [161]. In the case of multiple lesions, EEG/fMRI could theoretically help to determine the most active in the interictal period. Indeed, Jacob *et al.* [162] recently showed in a small group of five patients with tuberous sclerosis that the tuber could be responsible for extensive BOLD changes near or remote from the lesions, suggesting extensive spiking areas in these cases, and that some tubers could be identified as 'active' using this non-invasive method.

Paediatric studies

The feasibility of EEG/fMRI studies has been shown in several papers, even for very young children under 2 years. However, the HFR is different in different age groups, so that modelling strategies should consider using multiple specific HRF in young patients under 2 years old [156]. In a recent study including 13 children who underwent a 20-min EEG/fMRI acquisition at 3 T under sedation-induced sleep, BOLD responses were localized in the lesion or brain area presumably generating spikes in 84% of the cases [162]. In contrast with studies in adults, deactivations in the lesion and the spiking area were more common than activations.

Conclusion

Source modelling of EEG or MEG scalp signals and EEG/fMRI are both based on a modelling of bio-electromagnetic phenomena. As detailed in this chapter, each of them poses multiple methodological questions that have been progressively tackled and, for some of them, solved in the past few years. The question remains as to whether or not these new neurophysiological investigations have reached a sufficient level of reliability to be considered as usable in clinical routine for the management of patients suffering from partial epilepsies who are candidates to surgery, knowing that only those patients may draw an individual benefit from these investigations. The most obvious indication of spike source modelling in everyday practice is represented by lesional focal epilepsies, which have become much more frequent owing to the progresses of anatomical brain MRI, in particular for patients with multiple lesions. In such cases, predicting whether or not the patient will be seizure free after lesion resection is the question at stake, and a good spatial co-extensiveness between the lesion and the spiking area entails a favourable outcome prediction, even although a large scatter of spike sources is less reliable as predictor of a bad outcome. However, we fully adhere to the opinion expressed by Plummer *et al.* [111] in their recent review of EEG source localization that if 'the multimodal imaging technology on offer today for spike and seizure localization has limited value if its results are interpreted without due respect for the patients's electroclinical seizures', it remains that: 'EEG source localization is better regarded as an *underutilized* three-dimensional extension of traditional two-dimensional EEG analysis'. This latter statement is fully justified now that advanced source modelling software packages are commercially available. More advances are still needed to fully understand the coupling between the BOLD haemodynamic response and epileptic EEG transients, and thus to evaluate the reliability of EEG/fMRI data as markers of the epileptogenic zone. Furthermore, the question of whether or not lesional blood–brain barrier changes should be integrated in HRF modelling is still pending. Lastly, both techniques still suffer from the lack of prospective blinded validation studies on large groups of patients.

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67 Neuropsychological Testing in Presurgical Evaluation

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Introduction

Neuropsychological evaluation is an essential part of the comprehensive investigation of patients who are candidates for surgical treatment of epilepsy. The decision as to whether or not a patient is an appropriate surgical candidate is based upon data gathered by a team of professionals. Some of the necessary information is anatomical, derived from neuroimaging, some is physiological (electroencepalography) and some is based on clinical history and seizure pattern. Neuropsychology's contribution is unique in providing data about function through evaluation of a patient's strengths and weaknesses on cognitive tests. An important recent aspect of neuropsychological evaluation is the use of functional neuroimaging to localize critical sites for different cognitive functions in individual patients; this is beyond the scope of this chapter.

The information obtained through traditional neuropsychological testing methods is used in several ways. Interpretation of the pattern of results on neuropsychological tests gives information about the site of epileptic focus, inferred from the pattern of cognitive dysfunction. Although the sophisticated imaging techniques that are now able to evaluate brain structure and function overlap partially with neuropsychological information, they do not supplant it. With respect to localizing dysfunction, neuropsychological findings can reinforce or, if the findings disagree, question data from other sources about the site of seizure focus. When disagreement with other data occurs, those discrepancies can provoke further investigation. An unsuspected atypical representation of language is sometimes exposed in this way, and discrepant or unexpected findings from memory assessment can have a direct impact on surgical management, which will be discussed later.

Because neuropsychological results show the functional effect of a lesion or of abnormally discharging tissue, they allow evaluation of the impact of an individual's epilepsy on his/her life and provide a basis for counselling and making informed decisions. Preoperative neuropsychological measurements also form a basis for evaluating surgical outcome with respect to cognitive function by comparing pre- and postoperative performance on the neuropsychological tests. These objective data identify possible changes that can affect an individual's work, schooling or other activities. Knowledge gained from postoperative studies has also allowed another application of preoperative evaluation: prediction of surgery outcome in terms of seizure control and in terms of postoperative cognitive change/decline.

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Determination of site of dysfunction

A thorough neuropsychological evaluation requires 6–8 hours of direct contact between patient and examiner. A basic battery of tests should sample many different cognitive functions. If the battery were tailored for each patient from the outset, evaluations would be skewed to reflect the examiner's expectations. However, after exploring the whole brain with a comprehensive basic battery, the findings for individual patients can be pursued with further tests aimed at delineating that patient's cognitive profile more precisely.

A basic battery includes measures of intelligence, language, attention, memory, fronto-executive skills, visuospatial abilities, and some sensory functions and motor skills. Such an arsenal of tests taps function in the frontal and temporal lobes, and also parietal and more posterior regions. At its most fundamental level, the method underlying neuropsychological evaluation is to determine the dysfunctional *hemisphere* by comparing a patient's performance on verbal tasks with performance on visuospatial or visuoperceptual ones, and within the hemisphere to determine the dysfunctional *region* by comparing performance on various tasks. Results from this thorough, usually standardized, assortment of measures provide a reliable way of characterizing and quantifying the nature and degree of cognitive dysfunction arising from epilepsy. In this chapter, the emphasis will be on testing methods that are useful in focal, surgically treatable epilepsy.

Potential pitfalls in presurgical evaluation

Neuropsychological evaluation of unoperated epilepsy patients can be a challenge for a variety of reasons. Various demographic, medication and seizure-related variables have been shown to exert differential influences on performance. Some examples of demographic factors with a possible mediating role in neuropsychological functioning are gender and age, whereas seizure-related factors include age at onset of epilepsy, duration of disorder, seizure frequency, seizure spread, medications, etc. These factors should be considered when interpreting results from an individual's preoperative evaluation. One should also be aware that some neuro-

psychological tests used in epilepsy may be based on findings from patients with other kinds of brain pathology. Although principles of brain function and dysfunction are the same, different pathological processes can vary from one type of brain disorder to another, and extrapolating findings may not always be appropriate. Traumatic brain injury, neoplasms, vascular disorders, brain damage due to different toxic conditions, degenerative disorders of the nervous system, or infectious processes in the brain have specific features in terms of depth of lesion and involvement of cortical and/or subcortical structures, stability over time, presence of diffuse and/or distance effects, and presence of diseased or dead brain tissue [1].

Furthermore, the pathological substrate of epileptogenic lesions is itself heterogeneous. For example, the most frequent structural abnormality found in temporal lobe epilepsy (TLE) is hippocampal sclerosis. However, other neuropathological processes such as tumours, malformations, cerebrovascular accidents, trauma and infections are associated with epilepsy. It remains unclear whether or not hippocampal sclerosis and other seizure-inducing pathological processes at the same location may affect neuropsychological performance differently. Epileptic patients may or may not have discernible brain damage, and the existence of possible differential effects of lesional versus non-lesional TLE on neuropsychological performance remains an open question.

Another potential problem is that some information underlying neuropsychological clinical practice derives from operated patients, but cognitive effects of surgical lesions are not directly comparable to the effects of brain pathology generating seizures. Deficits are often more difficult to demonstrate in unoperated than in operated patients, possibly owing to such factors as the size of the lesion (larger in the case of surgical lesions) and uniformity of surgical versus heterogeneity of epileptogenic lesions.

A third problem encountered in the field is a relative lack of analogous verbal and non-verbal tests. The concept of hemispheric specialization is widely accepted in neuropsychological practice, and therefore verbal and non-verbal tests are commonly used for assessment of the dominant and non-dominant hemispheres, respectively. However, these tests have often been different in a variety of ways, introducing noise and interfering with direct comparisons of the functional abilities of the two hemispheres, especially in the clinical setting, where it is most important to compare results from the various tests within an individual patient. A strategy of using matched verbal and non-verbal tasks to study analogous brain regions in left and right hemispheres adds power to the neuropsychologist's ability to lateralize dysfunction and to analyse the nature of a patient's deficits. We consider this idea particularly important and will discuss it in more detail later.

Last but not least are the issues of clinical utility of neuropsychological instruments and the development and publication of norms for neuropsychological tests. The number of tests proven to be effective for presurgical evaluation of patients with epilepsy is not large. Tests that have been demonstrated to distinguish among different clinical groups may not be successful on the individual level, and even when a test can distinguish among patient groups with epileptogenic lesions of different locations, the questions of its sensitivity and specificity need to be answered. In addition, the field needs more published norms on its tests, to allow meaningful interpretation of results. Neuropsychological expertise depends on the use of sensitive tests and a solid database about those tests, and, happily, this is an area of growth in recent years.

Despite these caveats, the field has matured well over the past several years and there are many instruments in current use to evaluate patients for epilepsy surgery. We will provide a brief overview of some of these in the sections to follow, organized primarily by brain region.

Evaluation of frontal lobe function

Contemporary characterizations of frontal lobe functioning have shifted the emphasis from anatomically based descriptions (i.e. frontal or prefrontal lobe syndrome or signs) to functional ones, encompassing a variety of psychological constructs, with the concept of 'executive function' being a particularly prevalent descriptor. Definitions of this concept vary among authors, but most agree that some of the known functions of this brain region have to do with planning, initiation, organization, self-monitoring, self-regulation and decision-making. Measures commonly used to explore possible damage in the frontal lobes include tests of problem-solving, fluency, susceptibility to interference, planning and motor skills. Among the earliest objective measures were word fluency tests, which documented the clinically known paucity of spontaneous speech in patients with severe frontal lobe damage, and a card sorting test, which tapped several aspects of frontal lobe damage including problem-solving, impulsivity and inability to use cues to guide behaviour.

Problem-solving: Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) is part of the testing arsenal of most neuropsychologists. In the first studies using the WCST with epileptic patients, Milner [2] reported impairment in patients with resection from a frontal lobe, especially the left frontal lobe. The literature has now grown to contain many articles confirming or disputing the sensitivity of this task to frontal lobe dysfunction (for example see ref. 3). Furthermore, several studies have demonstrated that a significant proportion of patients with TLE display deficits on card sorting tests (for example see ref. 4). In a retrospective study [5] of WCST performance in 50 patients with unilateral resection from a frontal lobe (25 left, 25 right) and 40 patients (20 left, 20 right) with unilateral resection from a temporal lobe, we found no group differences before surgery, whereas postoperatively the left frontal lobe group performed worse than the right frontal and left temporal lobe groups but did not differ from the right temporal lobe group. Thus, poor performance on this task can occur in patients with dysfunction in the temporal lobe, in addition to the traditionally expected deficit after left frontal lobe damage. Interpretation of WCST results should be made cautiously, and should be viewed together with results obtained from other tests of frontal lobe function.

Generation of novel responses: word and design fluency

One implication from the card sorting data is that it may be difficult to detect deficits associated with right frontal lobe damage.

One of the rare measures shown to be able to capture dysfunction of the non-dominant frontal lobe is the Design Fluency Test (DFT) [6,7], which is used to measure fluency in the non-verbal mode. The task requirements are to create original abstract designs that do not represent anything and cannot be named, and to produce as many different designs as possible in 5 min. On average, healthy subjects produce about 16 acceptable drawings. Patients with right frontal lobe or right central lesions produce on average five or six acceptable designs, whereas patients with left frontal lesions, or left or right temporal lobe lesions, are not impaired [6]. The performance of patients with damage in the right frontal lobe is manifested in one or more of the following ways: a low overall output, a strong tendency to perseverate (producing many drawings that are essentially the same) and rule breaking (e.g. making representational drawings). Figure 67.1 shows three examples of design fluency: one from a healthy subject (Fig. 67.1a) and two from patients with a right frontal lobe lesion (Fig. 67.1b and c).

Several studies have shown that the DFT is characterized by very good intra- [8] and inter-rater reliability [8–10], and convergent and divergent validity [8]. Normative data for DFT have been published [9].

In contrast with their poor performance on the DFT, patients with a right frontal lobe lesion can do very well on verbal fluency tasks, and patients with a left frontal lobe lesion can perform well on figural fluency but poorly on word fluency. Comparing an individual's performance on paired verbal and visuoperceptual tasks that are as similar as possible except for the actual material of each task (e.g. words versus designs) aids in teasing out subtle deficits. In this case, comparing verbal to figural fluency within an individual patient can help determine whether or not there is frontal lobe abnormality, and can also point to the side of dysfunction. Asymmetry between left and right frontal lobe damage is easier to establish based on both tasks rather than on a verbal fluency task alone.

Susceptibility to interference

Flexibility is another important aspect of frontal lobe function, and it is often explored with Stroop tests [11], which in the 'interference condition' require inhibition of a well-practised response and production instead of a less automated one. The Stroop interference condition is sensitive to the effects of frontal surgical lesions, but does not consistently reveal dysfunction in patients with a frontal lobe seizure origin but no surgery. Lateralized effects on Stroop tests have not been demonstrated in epilepsy patients.

Planning: the Tower of London test

Tests of planning ability are among the staples for assessment of frontal lobe function. A measure that is widely used now is the Tower of London test [12]. It comprises a series of trials in which coloured beads must be moved from an initial position to a goal position in the smallest possible number of moves. For optimum performance, the sequence of moves should be planned before the first move is made. Whereas some studies have shown a clear impairment in patients with frontal lobe resection, and some have suggested a specific role of the left frontal lobe, others have found no differences between unilateral left and right frontal lobe surgery.

Motor tasks: strength: dexterity and coordination

Motor tasks are a useful part of diagnosing frontal lobe function. Among measures used are strength tasks using a hand or pinch dynamometer, manual dexterity tasks such as the Purdue or grooved pegboard tests, finger-tapping tests, and sequential unimanual and bimanual tapping (see ref. 1). Separate norms for men and women should be used when interpreting results from motor tasks, to take into account known significant gender differences. Age should also be considered, as performance declines on various motor tasks with advancing age [13]. Also important is the relationship between hand dominance and side of seizure focus [13], taking into account that the dominant hand is normally superior to the non-dominant hand. In general, an unusually large difference between the hands or a difference in an unexpected direction implicates dysfunction in the contralateral motor and/or premotor and prefrontal cortex.

Parietal lobes

Traditional tests of parietal lobe function have been useful primarily in patients with stroke, tumour or other large lesions. Demonstration of parietal lobe dysfunction in patients with epilepsy is more difficult, and the frank impairments associated with extensive lesions are not seen or are attenuated. Salanova *et al*. [14] described a series of 82 patients with non-tumoral parietal lobe epilepsy treated surgically at the Montreal Neurological Hospital between 1929 and 1988. Neuropsychological results were available in 30 preoperative and 27 postoperative patients from that series. Preoperatively, impairments in reproducing complex pictorial material, constructing block designs and/or left–right discrimination were found in nine (30%) of these patients, and contralateral visuospatial neglect while drawing was observed in two patients with right parietal lesions. After focal parietal resection, some of those patients showed new ($n = 7$) or exacerbated ($n = 2$) deficits that included dressing apraxia and difficulty identifying faces, and disturbances in spatial orientation, visuoconstructive functions and body image. Two patients also showed acalculia, anomia, agraphia and partial auditory and verbal agnosia. Thus, observable deficits occur in a minority of patients with parietal lobe epilepsy.

A retrospective look at our own preoperative and postoperative data on epileptic patients with highly focal damage confined to the left or right parietal lobe (eight left, five right) showed impairment in copying of the Rey–Osterrieth Complex Figure (ROCF) in those with a right parietal focus, whereas we found inefficient reading in those with a left parietal focus [15]. We also found raised thresholds contralateral to seizure focus for two-point discrimination on the palms of the hands in the right parietal group compared with the left. As with many other tasks, the difference was more pronounced after surgery.

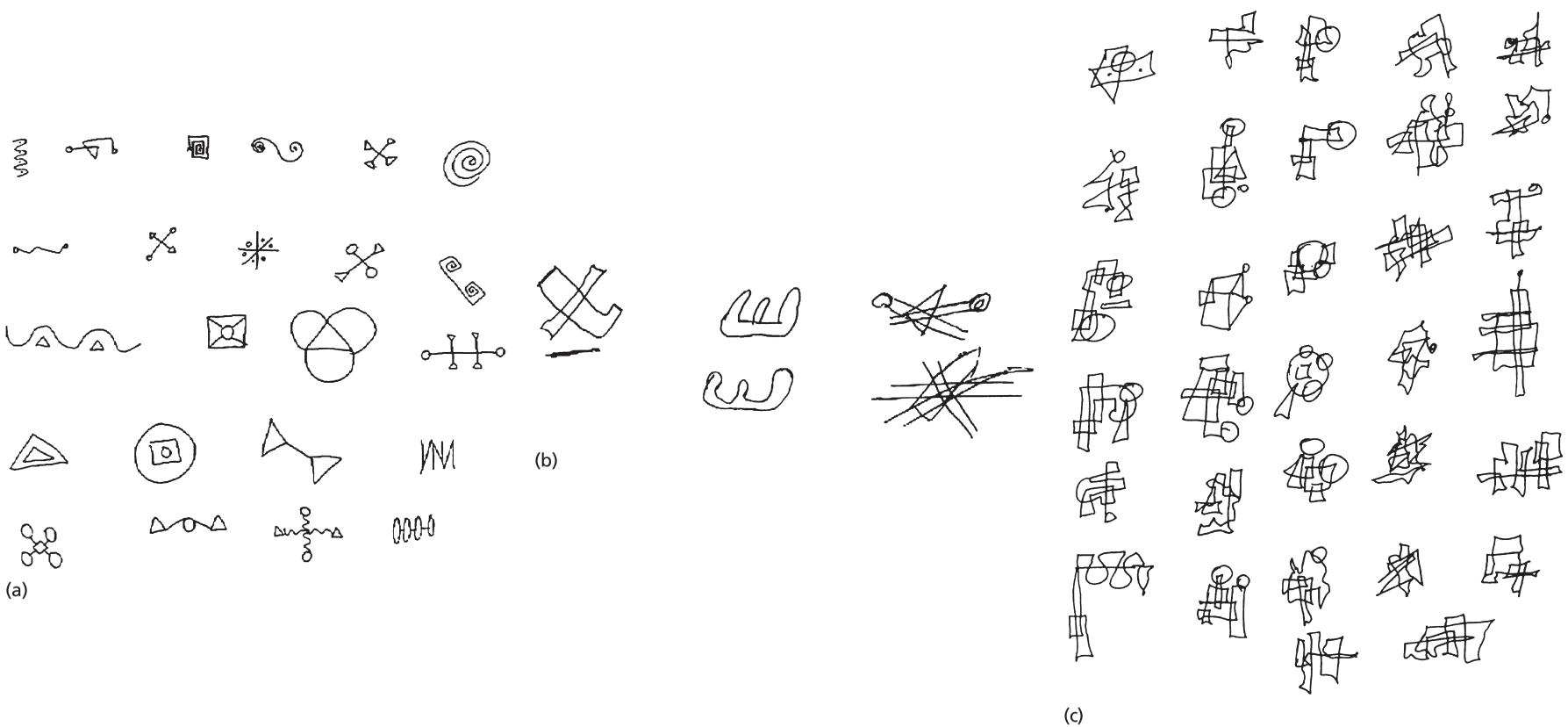


Fig. 67.1 Examples of drawings produced in 5 min in the DFT. (a) Productions made by a healthy control subject. This subject made three drawings that were discounted as perseverative (scoring not shown); producing a few such errors is normal. (b and c) Drawings made by two patients with right frontal lobe resection. (b) The patient, a clerk, had a full-scale IQ of 112. The underlined drawing represented a sculpture in his town, as did the drawing that resembles a rotated 'E'. In addition to these representational drawings, which are not allowed, the patient repeated one of the 'sculptures' (perseverative error), and the two remaining drawings were also highly similar to one another. This illustrates low output, rule-breaking and perseveration. (c) This patient, a geologist, had a full-scale IQ of 128. His output illustrates extreme perseveration: although he made many drawings, they are all alike.

Drawing upon findings from neuroimaging studies, one can expect tests of mathematical abilities to be sensitive to parietal lobe dysfunction, especially on the left side [16], and this avenue is currently largely unexplored. Difficult visuoperceptual tasks may also prove useful [17] and should be tried as part of neuropsychological evaluation.

To summarize, evaluation of parietal lobe function and dysfunction in epilepsy remains a challenge. It may be that most patients with a parietal lobe focus have abnormalities that are too subtle to be detected by existing neuropsychological tests. Among the measures currently available, those that test visuoconstructive and visuospatial functions, reading, and somatosensory functions seem to be the best. A direction for growth in the field is to develop new instruments for evaluation of this brain region based on these best existing measures and on neuroimaging findings.

Occipital lobes

An occipital lobe focus is rare in epilepsy, and therefore little effort has gone into developing special tests of occipital lobe dysfunction for epileptic patients. Tests of visual perception that are available include tests of visual (in)attention and scanning (cancellation and line bisection tests), colour processing (perception, recognition, naming), face recognition and discrimination, visuospatial processing (Benton Judgment of Line Orientation, Hooper Visual Organization test) and visual interference (hidden and overlapping figures tests). These instruments offer evaluation of visual and/or visuospatial functioning with minimal or no engagement of the motor system. Although deficits on some of them have been associated with right posterior cerebral lesions [18], the findings have not always been consistent and cannot be considered specific to the occipital lobe. Furthermore, the clinical utility of these tests in preoperative evaluations of patients with epilepsy remains questionable, given the lack, or inconclusiveness, of published findings.

Temporal neocortex

Although memory is the hallmark of medial temporal lobe function, several other types of measures are also used to assess the temporal neocortex. Among the most important of these are word-finding tests, a very commonly used example of which is the Boston Naming Test (BNT) [19,20], which requires naming pictures. We demonstrated a deficit on the BNT preoperatively in patients with left, but not with right, TLE [21], as did Hermann *et al*. [22], whose patients with left TLE were also impaired on repetition, comprehension and reading. In contrast, Saykin *et al*. [23] also reported a left TLE naming deficit, but verbal fluency, repetition, comprehension and reading were preserved in their patients. A newer test of naming in response to word definitions instead of to pictures, introduced by Hamberger *et al*. [24], approximates the experience of word-finding difficulties more closely than do tests of picture-naming, and it has been shown to tap a more anterior area of the left temporal lobe, making it a more appropriate test of the region to be excised in temporal lobe surgery [25].

One of the most widely used tests of language comprehension is the Token Test [26]. Reports on Token Test results in unoperated epilepsy patients are conflicting. For example, Hermann *et al*. [22] reported impairment of patients with left TLE compared with those with right TLE on this test. However, our analysis of 131 patients with focal cortical resection from a left or right temporal, frontal, parietal or occipital lobe revealed an impairment in all preoperative patients with a left- compared with right-sided focus and no difference among the sites within the left hemisphere (unpublished data). In contrast, Giovagnoli [27] found that patients with left or right temporal or extratemporal epilepsies all performed within a normal range on the Token Test.

For the non-dominant temporal neocortex, tests meant to tap complex visuoperceptual functions are frequently included, as visual association cortex is part of the temporal lobes. The most widely used visuoperceptual tests include the Hooper Visual Organization test, Benton Judgment of Line Orientation test, and Benton Face Recognition test. For these and similar tests, an association with a particular site (lobe) within the brain has not been consistently demonstrated. For example, patients with left versus right TLE do not differ on the Benton Face Recognition test [28], or on the Hooper Visual Organization test or Judgment of Line Orientation test [29]. Thus, the use of existing visuoperceptual tests remains a problem because deficits do not arise exclusively from one site and side within the brain.

Medial temporal lobe function: memory assessment

A thorough evaluation of memory is particularly important in the assessment of epileptic patients because the majority of surgical candidates have a temporal lobe focus, and memory is the most salient of temporal lobe functions. It is well known that bilateral lesions in the medial temporal lobe can result in severe global memory deficits [30], but such profound memory impairment is rare. In contrast, patients with unilateral temporal lobe dysfunction show a more restricted, material-specific deficit. Therefore, a thorough memory assessment should address each hemisphere with tasks appropriate to its specialization.

The fundamental difference between the two temporal lobes is well known. The left (dominant) temporal lobe mediates memory for verbal material, such as names, word lists, stories or number sequences, and the right temporal lobe mediates memory for material that cannot be verbalized readily, such as faces, places, abstract designs or music. Because of this difference in the kind of material each temporal lobe mediates, memory tests ideally should be as purely verbal, or purely non-verbal, as possible. In this way we attempt to maximize differences between the hemispheres by using memory tasks that are polarized into the verbal or non-verbal domain, and in doing so we increase the probability that our tests tax primarily one temporal lobe.

Traditional memory tests

Most neuropsychologists working in epilepsy programmes use memory tests from published batteries [31], especially those in the Wechsler Memory Scales (WMS), and most also use the Rey–Osterrieth Complex Figure test [32,33]. The latter consists of a complex geometric design that patients must copy, followed by a free recall test that may occur immediately and/or after a delay. The copy task provides useful information (see section on the parietal lobe, above) but memory results are at best contradictory. Some group data show impairment after right temporal lobe damage, whereas other group data show no difference between left and right temporal lobe damage. The usefulness of the memory task for individual cases is thus very limited. Several different verbal tasks, usually involving paragraph memory or list learning, are also used widely and will be discussed later in this chapter.

Most of the information available from earlier studies about memory performance of patients with TLE was based on postoperative results in patients who had undergone resection from a temporal lobe. Those results do not necessarily generalize to the unoperated case. We examined the performance of unoperated patients with TLE on several commonly used memory tests, using measured MR scans to group the patients according to side of hippocampal atrophy. The tasks studied were the logical memory (or prose passages), associate learning (word pairs) and visual reproduction (designs) subtests from the WMS and the Rey–Osterrieth Complex Figure test described earlier in the chapter. Figure 67.2 shows the mean recall scores of the two patient groups on the four measures after a 90- (WMS tests) or 45-min (Rey–Osterrieth Complex Figure test) delay. There were no significant differences between the left- and right-sided atrophy groups on any of these measures [34].

As these have been the most widely used memory tests in the evaluation of epilepsy surgery candidates, results from them are frequently reported in the literature. In a meta-analysis of studies reporting memory data in epilepsy, Lee and colleagues [35] were limited to analysing WMS findings because only WMS data were plentiful enough to allow a large analysis. Their findings were clear: the WMS tests did not differentiate left versus right temporal lobe groups. In a combined study by seven epilepsy centres, Barr *et al*. [36] analysed results of 757 left or right temporal lobe presurgical patients on the Visual Reproduction subtests of the WMS and on delayed recall of the Rey–Osterrieth Complex Figure test. Despite their large sample, they also found no differences in these measures between patients with left versus right TLE.

These findings are hardly surprising. Those tests are outdated and psychometrically naive, and not one of them is strongly polarized into the verbal or non-verbal domain. Furthermore, except for the WMS paired-associates test, the recall tests shown in Fig. 67.2 occurred after a single exposure to the material to be remembered. Effects of attention, comprehension and individual strategies are probably most variable on a first trial, or on an only trial, and these effects can confound memory findings.

Matched verbal and non-verbal learning and memory tests

We compared the performance of the patients of Fig. 67.2 with severe left or right hippocampal atrophy on two tasks that tested learning over the course of four trials. The tasks [34,37] were matched in paradigm, differing only in the type of material to be learned: 13 abstract words in one and 13 abstract designs in the other (Fig. 67.3). On each learning trial, subjects copied the 13 items, which were shown one at a time, and immediately upon

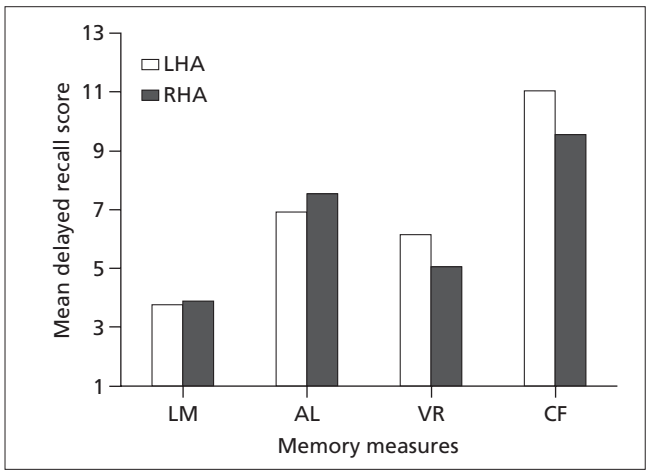


Fig. 67.2 Mean delayed recall scores of patients with left or right hippocampal atrophy on three WMS tasks and on the Rey–Osterrieth Complex Figure (CF). LM, Logical Memory, maximum score 23; AL, Associate Learning, maximum score 10; VR, Visual Reproduction, maximum score 14; CF, Rey–Osterrieth Complex Figure, maximum score 36; LHA, left hippocampal atrophy group; RHA, right hippocampal atrophy group.

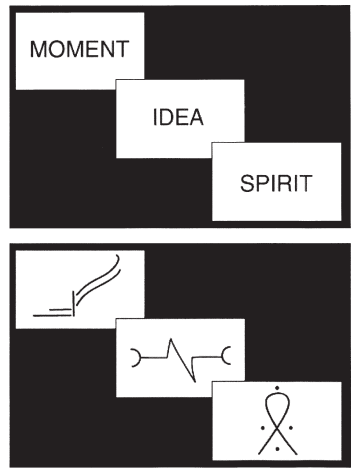
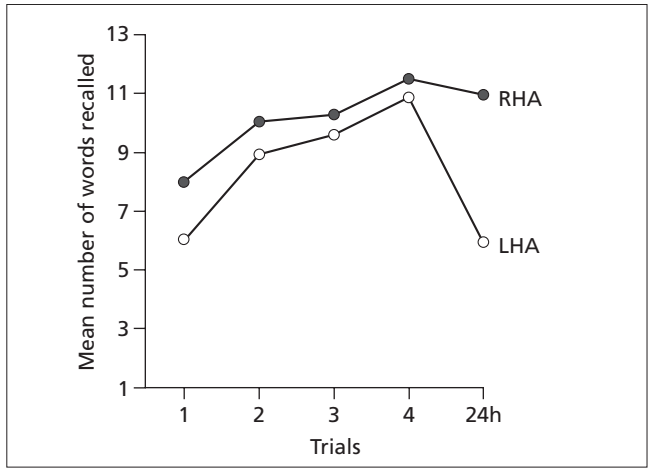


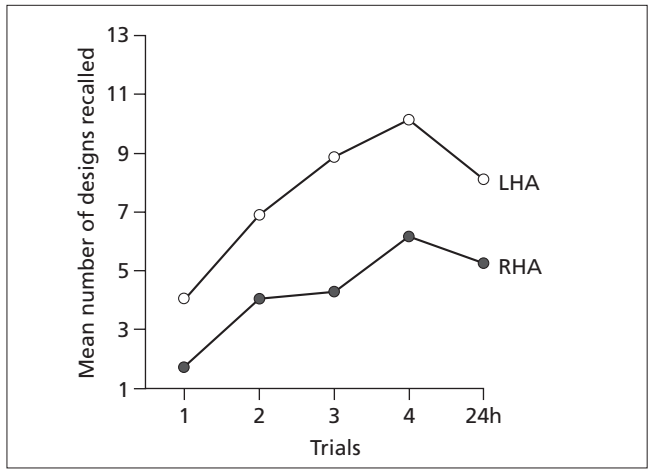
Fig. 67.3 Examples of stimuli from the matched learning tasks: Abstract Word List learning (AWL) and Abstract Design List learning (ADL). The ADL is administered before the AWL. During the learning phase, stimuli are shown one at a time while subjects copy them; each learning trial is followed by a free recall test, and an additional delayed recall test is obtained 24 h later.

completion of the copy task they wrote as many words or drew as many designs as they could remember. A delayed recall was obtained 24 hours later.

On these tests there was a clear difference between patients with left hippocampal atrophy and those with right in the pattern of results [34]. On the verbal task, the patients with left hippocampal atrophy were worse than those with right hippocampal atrophy, in that they showed severe forgetting of the words after the delay interval (Fig. 67.4a). In contrast, the patients with right hippocampal atrophy were worse than those with left on the non-verbal task, in that they were slow and inefficient during the learning phase (Fig. 67.4b). Thus, patients with left hippocampal atrophy were impaired in *retention* but not learning of words, whereas right hippocampal atrophy patients showed deficient *learning* of designs but they did not forget what they had learned.



(a)



(b)

Fig. 67.4 (a) Learning (four trials) and 24-h delayed recall of abstract words in patients with left or right HA. Maximum score on each trial is 13. (b) Learning and delayed recall of abstract designs in patients with left or right HA. Maximum score on each trial is 13. LHA, left hippocampal atrophy group; RHA, right hippocampal atrophy group.

These results show a double dissociation in unoperated patients for verbal versus non-verbal material in two tasks that were identical except for the nature of the material. This finding contrasts sharply with the lack of effect in the four measures reported above. The critical features of these more sensitive tasks are:

- The material used is polarized: the abstract words are highly verbal and the abstract designs are highly non-verbal.
- These are learning tasks, providing the possibility to improve with additional exposure to the material, increasing the difference between people with a true learning deficit and those who do poorly on a first trial for other reasons.
- They are matched, varying only according to the verbal versus non-verbal nature of the material. This allows direct comparison of the efficiency of the two hemispheres, even within individual patients.

These examples illustrate the importance of the choice of tasks in neuropsychological testing. Several matched memory tasks have been developed in recent years [38,39]; this often represents development of a non-verbal analogue for a previously existing verbal test such as the Rey Auditory Verbal Learning Test (RAVLT) [40,41], the California Verbal Learning Test (CVLT) [42], the Buschke Selective Reminding test [43] or the modified Brown–Peterson paradigm [44,45]. Although some results in presurgical epilepsy patients have been published and may be described as encouraging, these tests await further empirical confirmations.

The Warrington Recognition Memory (WRM) test is a matched pair of tasks using words and faces; it was reported to be sensitive to the effects of temporal lobe lesions in patients with neoplasms and infarctions [46] and in resected patients with TLE [47]. However, other studies showed its clinical utility for presurgical epilepsy patients to be very limited (for an example see ref. 48). Baxendale [48] suggested that temporal lobe lesions that extend beyond hippocampus may be necessary to produce deficits on the WRM. Its modest diagnostic efficiency in focal epilepsy may be due to its use of an incidental memory paradigm with a single exposure to the stimuli and to memory being tested immediately after presentation of the stimuli.

The fact that the WRM does not reliably differentiate left and right temporal lobe dysfunction despite using paired tasks adds emphasis to the utility of the paired learning tasks illustrated above [34,37]. Those tasks alerted us to the difference in pattern as well as in material that distinguishes the left and right temporal lobe memory deficits. Some findings obtained by other authors and using different testing paradigms are consistent with the idea that deficits from unilateral temporal lobe lesions may be both material and process specific. For example, several independent groups reported impaired recall but not impaired learning of words in those with left TLE compared with those with right TLE and healthy control subjects [49,50]. Furthermore, some authors who examined non-verbal learning reported a deficit in the learning of non-verbal material but not in its retention in patients with right TLE [51,52].

Other verbal learning and memory tests

There is a growing literature on single tasks that seem to be sensitive to verbal memory deficits in unoperated epilepsy patients.

Those used most frequently (besides WMS subtests) are the RAVLT and the CVLT, both of which comprise word lists that are presented over several trials, an interference list that is presented once, and recall trials obtained after interference and after a delay. Published results from these tests suggest that they can distinguish between left and right TLE [53].

A promising test that taps a more everyday life aspect of memory is the Story Learning Test developed by Frisk and Milner [54]. It consists of repeated presentation of a story until it is learned to a criterion: therefore it provides measures of learning and of immediate and delayed retention. In the original study, patients with left temporal lobe excisions were impaired compared with those with right temporal lobe excisions and healthy control subjects [54]. We have used the test with unoperated patients for several years, with excellent results that differentiate patients with left TLE from those with right TLE and control subjects [55]. Furthermore, we have developed three alternative test forms and demonstrated their equivalence within two languages (J. Djordjevic, M.L. Smith, V. Sziklas, D. Piper, S. Pénicaud, M. Jones-Gotman, McGill University).

Non-verbal learning and memory tests

Since the old non-verbal memory measures had little success in detecting right temporal lobe damage, there have been a number of attempts to modify the existing tests or develop new procedures to evaluate non-verbal memory. Helmstaedter *et al*. [56] introduced a six-trial learning test in which five line designs had to be reconstructed using wooden sticks. The authors reported learning deficits in patients with right but not left TLE [56]. More recently, Gleissner *et al*. [52] compared performance on this test in patients with right TLE with and without hippocampal sclerosis or atrophy. They found impaired learning only in the patients with right hippocampal atrophy.

Barr [28] reported a deficit in unoperated patients with TLE on the Denman Face Recognition Test. To our knowledge, this finding has not been replicated, and we have been unable to replicate it in our TLE patients. This was not surprising, however, as that task tests memory after a single exposure. We now use a face-learning task ('the Twins Test') [57] consisting of four trials to learn 12 unfamiliar faces, and a delayed recognition test 24 h later. In our original study of patients with a temporal lobe resection we found a learning impairment in the right resection group and no difference between the left resection and normal control groups. The right temporal deficit was specific to learning, with no greater forgetting after a delay than in the other groups, which was similar to our design-learning task as reported earlier in the chapter.

Tests of spatial memory have been shown to be sensitive to right TLE. For example, Baxendale and colleagues [58] and Abrahams and colleagues [59] have both reported deficits in right TLE groups compared with patients with left TLE on spatial memory tasks, confirming findings previously documented in patients with surgical excision.

We have emphasized the usefulness of newer tasks and the importance of using tasks that have been shown to be sensitive to unoperated patients with epilepsy. We maintain that the development and validation of original testing procedures and replacement of old measures with new and more sensitive ones is a desirable activity in the field. Although the existence of a variety of testing procedures prevents direct comparisons of results across centres, we believe that the possible gains outweigh the disadvantages. A search for better tools is more important than uniformity, and the development of efficient instruments will best enable the advancement of the field.

Intracarotid anaesthetic procedures

For some 50 years the intracarotid amobarbital procedure has been an important part of the preoperative evaluation of patients who are candidates for surgical treatment of epilepsy. Its usefulness has come increasingly into question, especially as neuroimaging techniques have improved. Problems with access to amobarbital also led to the use of other anaesthetizing agents and therefore to a change in nomenclature to the more generic intracarotid anaesthetic procedure (IAP).

Description of procedure

Details of the IAP differ among centres, but the basic core is similar across institutions. It consists of the injection of a barbiturate, still usually sodium amobarbital, into one hemisphere, most often through the internal carotid artery; a few centres perform selective and superselective procedures into other vessels for selective inactivation of hippocampal structures [60,61] but these are less common. This anaesthetizes the injected hemisphere and allows one to test the abilities of the awake hemisphere in isolation. The effect is short, and is usually dissipated after about 5–8 min. During the effect, simple speech and memory tests are performed. The injection is made by a radiologist and is preceded by a 3-mL angiogram to verify that there is no serious vascular anomaly and to predict the distribution of the drug. In most institutions an electroencephalogram (EEG) is obtained during the test, and is either read online or recorded on computer for interpretation later by an electroencephalographer.

Before injection, basic speech and memory tests are performed to establish a baseline. Upon injection, more speech and memory tests are carried out while one hemisphere is inactivated. Memory testing consists of showing new material while only one hemisphere is functional, and then testing memory for that material later when the drug is no longer active and both hemispheres are back to baseline functioning. Speech tests are kept simple and usually include naming, serial or automatic speech (such as counting and reciting days of the week), comprehension, reading and repetition [62].

In some institutions all patients undergo an IAP, whereas in others it is performed only if atypical cerebral dominance for language is suspected or if there is evidence of bitemporal dysfunction and consequently a potential risk of significant memory loss after temporal lobe surgery.

Atypical language dominance is suspected in patients who are left-handed, who have a strong family history of left-handedness, who do not show the usual right ear dominance on dichotic listening tests, and/or whose pattern on cognitive tests indicates dysfunction in the hemisphere opposite to a lesion or focus identified by clinical signs, neuroimaging or electroencephalography.

Bitemporal dysfunction may be suspected in several ways. Impairments on both verbal and non-verbal memory tests in the basic, non-invasive clinical memory evaluation suggest bitemporal abnormality. Evidence from electroencephalography or neuroimaging pointing to bitemporal abnormality is also grounds for carrying out an IAP, as are discordant findings about the focus from electroencephalography, MRI and/or neuropsychological assessment.

Interpretation of intracarotid anaesthetic procedure results: language dominance

Interpretation of the speech tests is most often unambiguous: if the dominant hemisphere is injected the patient is aphasic while the drug is active, whereas if the non-dominant hemisphere is injected the patient continues talking without significant errors. Several different patterns may be observed in bilateral speech representation. These include disruption of all speech functions after injection in one hemisphere, with minor but significant disruption after injection in the other; dissociation of type of disruption (for example naming in one hemisphere and comprehension in the other), equal and significant disruption in both hemispheres, and no obvious disruption in either hemisphere [63].

Interpretation of bilateral speech differs among institutions and individuals; consequently, reports of the incidence of this type of atypical language organization vary [64]. This is of considerable theoretical interest but it does not impact significantly on patient management, because the most critical practical question, 'Is there significant language function in the hemisphere destined for surgery?', can almost always be answered.

Interpretation of intracarotid anaesthetic procedure results: memory

A basic assumption underlying the memory application of the IAP is that the patient will have to rely on the awake hemisphere to remember material shown while the drug is active. The patient will not remember the material if the awake, or non-injected, hemisphere is damaged in areas important for memory. The crucial test is after injection of the hemisphere destined for surgery, because it tests the memory function of the hemisphere that will be left intact; thus, results of that injection are expected to predict how well memory will function after resection from the injected temporal lobe. Injection opposite the hemisphere destined for surgery is also important, as the result should confirm or disconfirm an expected dysfunction in that hemisphere. *Good* memory after injection opposite a temporal lobe targeted for surgery is another meaningful result. It shows that the temporal lobe, and presumably the hippocampus planned for resection, functions well, and warns that the deficit after such surgery may be larger than what is typically seen.

It is assumed that passing the IAP memory test requires adequate hippocampal function. Therefore, performance on the test can affect surgical planning. In some centres, patients who show significant forgetting in the critical test receive a limited resection that spares the hippocampus or encroaches only modestly upon it. More rarely, surgery is denied altogether to such patients. There is no current standard for defining failure; some centres have a cutting score and others compare the performance from the two injections, making a relative rather than an absolute judgement [65]. It is important also to take language dominance into account when interpreting IAP memory results, because in most patients there is a bigger drug effect in the dominant than in the non-dominant hemisphere [66]. This results in smaller differences between ipsilateral-to-focus and contralateral-to-focus injections when the focus is in the dominant hemisphere than when it is in the non-dominant hemisphere. As resection from a well-functioning hippocampus can result in a more marked postoperative memory loss than resection from a dysfunctional one [67,68], IAP memory performance, both ipsilateral and contralateral to proposed surgery, should be taken into account in decisions regarding hippocampal excision.

Intracarotid anaesthetic procedure issues

Several controversies and issues have arisen in the past concerning the IAP. They include questions about the extent to which critical memory regions are affected by injection into the internal carotid artery, given that it does not irrigate the posterior hippocampus, and questions about the true risk of amnesia in patients who fail an IAP memory test, given that many of them undergo partial hippocampal resection and do not become amnesic. Other issues involve the timing of presentation of memory stimuli after injection, the number and type of stimuli used, determination of drug dosage and the effect of different dosages, and dealing with fluctuations in attention. These topics are discussed in a special issue of *Brain and Cognition* [volume 33 (1&2), 1997] devoted to the IAP, and in a recent textbook chapter [69].

Around 10 years ago two serious problems occurred with amobarbital. One problem was that in a certain number of procedures injection of this drug produced no effect or a reduced one. According to Bookheimer and colleagues [70], this occurred in patients whose antiepileptic drugs had carbonic anhydrase-inhibiting properties – in particular topiramate and zonisamide. Those authors showed a reduced anaesthetization in one patient even 5 weeks after discontinuation of topiramate, and they therefore recommended discontinuing those drugs for at least 8 weeks before performing an IAP.

The second problem was that there have been recurring shortages of amobarbital over the years, with a particularly long-lasting one that in 2001 resulted in many centres looking for alternatives to this drug. Methohexital had already been used by a few centres for some years [71], and propofol was tried in a small number of patients [72]. Methohexital has the disadvantage that it is very short-acting and usually must be reinjected within a procedure, whereas propofol is contained in an oil-in-water emulsion and is thus also not an ideal choice. At the Montréal Neurological Institute we rejected those possible alternatives and opted to use etomidate, which is an imidazole derivative and a potent non-barbiturate hypnotic agent [73]. With the new drug we also introduced a change in the procedure, which we call the etomidate speech and memory test (*e*SAM); after injecting an initial bolus, we maintain the full hemianaesthesia by infusion of the drug, which is terminated only after all speech tasks have been sampled and all critical memory items

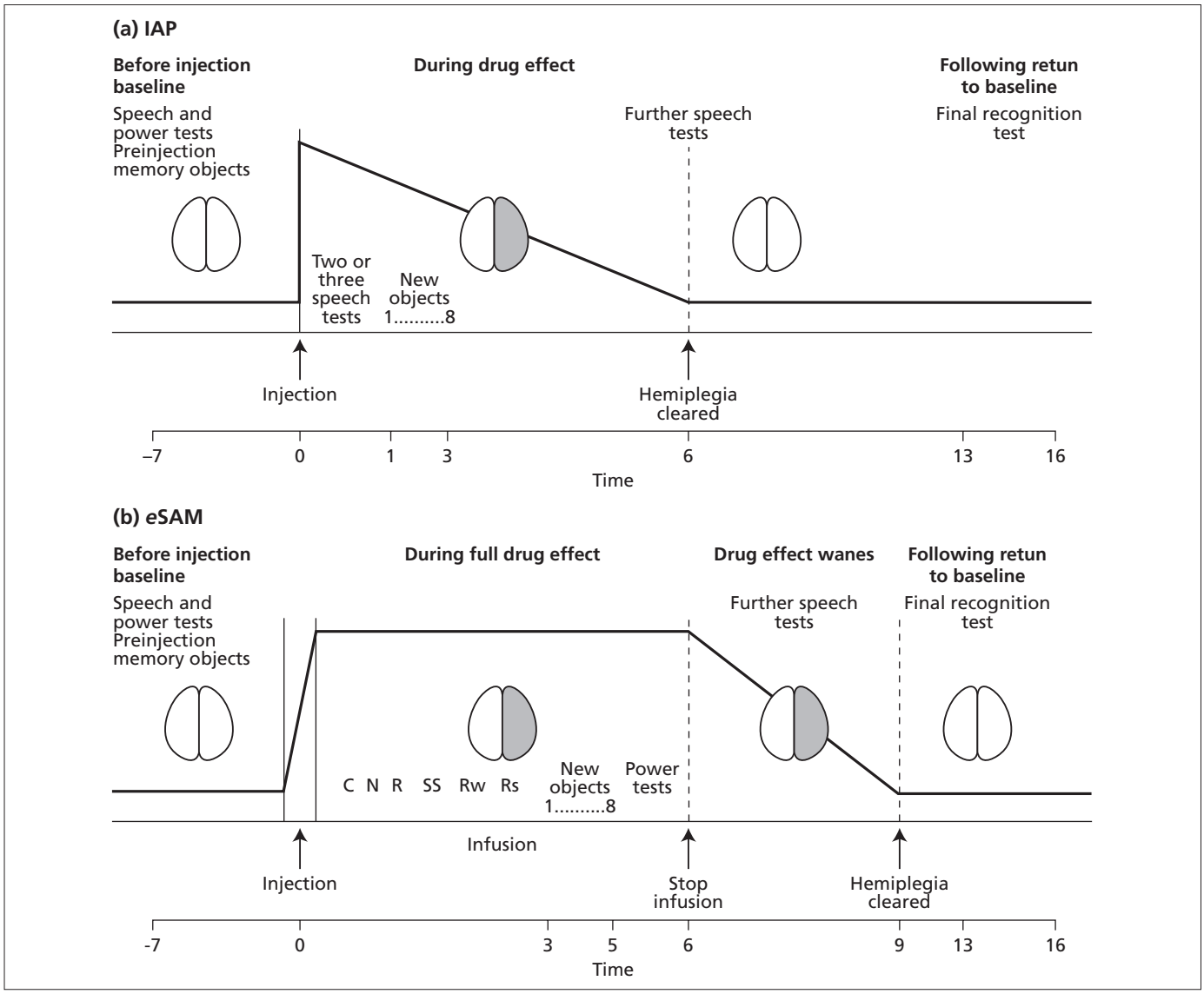


Fig. 67.5 Comparison between the traditional intracarotid anaesthetic procedure (IAP) and etomidate speech and memory (eSAM) procedure. During the IAP, the effect of the drug begins to wane immediately after the initial bolus, so task presentation must be rushed. In contrast, during eSAM maintenance of the drug infusion after the initial bolus over the period of time needed to complete one round of language tests and present all eight memory objects allows well-timed and controlled presentation of the critical cognitive tasks while the drug is fully active. C N R SS Rw Rs denotes the language tests: comprehension, naming, reading, serial speech (counting, reciting days of the week), repetition of words and repetition of sentences.

have been presented (Fig. 67.5). As a result of the changed procedure, we have had no instances of inability to interpret memory results [74], which is frequently a problem in the traditional IAP owing to return of function before all memory items have been shown.

Non-invasive procedures

Non-invasive alternatives to the IAP have been and are still being developed. The most progress has been made in determination of language dominance using positron emission tomography [75] to some extent, and functional magnetic resonance imaging (fMRI) [76,77] to a greater extent. fMRI is used by a growing number of centres to supplement or to replace the IAP in determining cerebral dominance for language [78], but development of a viable alternative to the IAP memory test has been more challenging. However, recently a few paradigms have been reported to produce reliable results [79,80]. These paradigms must be thoroughly validated before one can consider replacing the IAP with them, and once the methodology is considered reliable some patients will still require an IAP instead. Those would be patients

who are not capable of performing the cognitive tasks required in activation neuroimaging, who are unable to go into a scanner because of claustrophobia or metal parts in their bodies, or who are unable to spend the necessary amount of time in the scanner because of frequent seizures. In addition, an important argument against a total replacement of the IAP is that only the IAP mimics, and therefore predicts, the effects of surgery because it transiently disables most of one hemisphere.

Conclusion

Neuropsychological evaluation in epilepsy assesses cerebral function widely to determine dysfunctional regions and also to predict the effect of surgery on postsurgical function. We have described some tests used for this purpose, emphasizing those that we believe are best suited and explaining why. We noted that older tests too often cannot reliably detect a seizure focus in unoperated patients and suggest that such measures were inappropriate because of their lack of sensitivity. However, an increasing number of newer tasks succeed in demonstrating neuropsychological deficits in focal epilepsy. Therefore we recommend that clinicians and researchers attempt to seek and/or develop appropriate instruments specifically for this field, and we have pointed out areas of greatest need for growth. Overall, our appraisal of the current state of neuropsychological assessment in the evaluation of patients with epilepsy is very positive. Results from these evaluations continue to contribute to decisions about patient management in general and with respect to feasibility of surgery, extent of surgery and cognitive outcome after surgery.

Acknowledgements

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68 Presurgical Psychiatric Evaluation

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Introduction

In the last three decades, epilepsy surgery has revolutionized the treatment of pharmacoresistant epilepsy, with anterotemporal lobectomy (ATL) constituting the most frequently performed surgical procedure. Postsurgical psychiatric complications have been reported with increasing frequency in the last decade. Yet, in most epilepsy centres, presurgical evaluations rarely include a psychiatric evaluation to identify patients with past and present psychiatric comorbidities, and therefore patients at risk of postsurgical psychiatric complications. Indeed, in a survey sent to the 88 major epilepsy centres in North America, only 21% of the 47 centres (53%) that completed the survey routinely performed a psychiatric evaluation in *every* presurgical candidate. Three centres (6%) perform a psychiatric evaluation only in case of a previous serious psychiatric history, 16% perform a psychiatric evaluation if recommended by the neuropsychologist and 45% follow either of the last two criteria. The purpose of this chapter is to examine whether or not presurgical candidates should undergo a psychiatric evaluation and specifically to assess the impact of presurgical psychiatric disorders on postsurgical psychiatric complications, employment and seizure outcome. The last section of the chapter provides protocols for presurgical psychiatric evaluations.

Are surgical candidates at risk of postsurgical psychiatric complications?

Presurgical psychiatric comorbidity

Compared with seizure-free patients and normal control subjects, patients with medically intractable epilepsy are at risk for mood, anxiety and psychotic disorders, and attention deficit hyperactivity disorder (ADHD). In fact, various case series have found lifetime prevalence rates of depressive disorders ranging between 30% and 50%, those of anxiety disorders between 10% and 30% and those of ADHD between 20% and 30% [1–4]. In a review of the literature Koch-Stoecker found prevalence rates ranging from 43% to 80% among seven case series [5]. In the case series from the Bethel Epilepsy Center, 43% of patients met criteria for a discrete psychiatric disorder (i.e. mood, anxiety or psychotic disorder) according to the *Diagnostic and Statistical Manual of Mental Disorder* (3rd edn, revised; DSM-III-R) criteria, while an additional 29% met criteria for a psychiatric syndrome and personality disorders.

Postsurgical psychiatric complications

Postsurgical psychiatric complications can be the expression of a *de novo* psychiatric disorder, a *recurrence* of psychiatric disorder that had been in remission for a period of time prior to surgery, or an *exacerbation* in severity of a psychiatric disorder of mild severity that had gone unrecognized by patient, family and clinician or that was identified because of a more careful evaluation of the patient.

Postsurgical psychiatric complications of epilepsy surgery were reported initially in 1957 by Hill *et al.* [6], who described depressive episodes occurring independently of seizure outcome and which remitted within 18 months. The most frequent postsurgical psychiatric complications include depressive and anxiety disorders and, less frequently, psychotic disorder. Psychogenic nonepileptic events (PNEEs) and other types of somatoform disorders have also been identified with relatively low frequencies.

Postsurgical depressive and anxiety disorders

The prevalence rates of postsurgical depressive disorders have ranged from 5% up to 63% among various studies. More often than not, these postsurgical complications are an expression of a *recurrence* or *exacerbation* of a presurgical mood disorder, whereas *de novo* depressive disorders are less frequent and are also likely to occur in the first 6 months after surgery. For example, Wrench *et al.* [7] published a study of 62 patients who underwent epilepsy surgery: 43 had an ATL and 19 an extratemporal lobectomy (ETL). Both groups had similar presurgical histories of depression and anxiety (33% and 23%, respectively, for ATL and 53% and 18%, respectively, for ETL). At 1 month after surgery, symptoms of anxiety and/or depression were reported by 66% of ATL patients and 19% of ETL patients; at 3 months, 54% of ATL and 33% of ETL patients were still symptomatic with 30% of ATL and 17% of ETL patients still experiencing a depressive episode. By that time, 13% of ATL patients had developed a *de novo* depressive episode and 15% a *de novo* anxiety disorder, whereas 18% had developed other types of *de novo* psychiatric disorders. In contrast, only 17% of ETL patients had developed *de novo* anxiety, but not depression or other psychopathology. Of note, there was no significant association between postsurgical psychopathology and seizure outcome at the 3 months' follow-up.

In a study of 49 patients who underwent an ATL and were followed for a period of almost 11 years, Altshuler *et al.* [8] found

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that five patients (10%) developed *de novo* depressive episodes, four within the first postsurgical year. Similar findings were reported by Ring *et al*. [9] in a study of 60 consecutive patients who underwent an ATL and had a psychiatric evaluation prior to surgery and at 6 weeks and 3 months after surgery. At 6 weeks, 45% of all patients experienced emotional lability and anxiety, 22% of whom had not experienced such symptomatology before surgery. By 3 months, symptoms of emotional lability and anxiety had remitted or improved significantly but not so the depressive states.

Blumer *et al*. [10] reported a much higher prevalence rate of *de novo* psychiatric complications in a study of 50 consecutive patients, 44 of whom underwent an ATL and six a frontal lobe resection; 14 patients (32%) developed *de novo* psychiatric disorders presenting as an interictal dysphoric disorder in six patients, depressive episodes in two and a psychotic disorder in six, while only three patients (7%) experienced an *exacerbation* of a presurgical interictal dysphoric disorder. In all but two patients the psychiatric complications occurred within 2 months after surgery. All psychiatric complications remitted with psychotropic treatment. Of note, these investigators associated the development of postsurgical psychiatric complications with persistent seizures. Glosser *et al*. [11] published a study of 44 patients who underwent an ATL; in the first month after surgery 12 patients (31%) developed *de novo* depression and/or anxiety disorders or recurrence of a disorder that had been in remission during the 6 months preceding the surgical procedure. By 6 months they were still symptomatic but significantly improved, and by 1 year all but two patients had become free of symptoms.

A study completed at the Rush Epilepsy Center included 100 consecutive patients, 60 men and 40 women, who had undergone an ATL and were followed for a minimal period of 2 years (median follow-up duration 8.3 ± 3.0 years; range 2–13 years) [12]. Fifty-six patients had a presurgical lifetime psychiatric history, 46 of whom had a mood disorder that consisted of depression alone in 21 patients, and mixed depression and anxiety disorders in 25 patients, while three had in addition ADHD. Forty-four patients met our criteria for postsurgical psychiatric complications: nine patients (11%) experienced a *de novo* depressive/anxiety disorder and four patients (4%) experienced a *de novo* psychotic episode. Thirty-one patients experienced an *exacerbation* in severity of presurgical depressive/anxiety disorders; these complications occurred during the first postsurgical 12 months. In addition, 7 out of these 31 patients developed *de novo* psychogenic non-epileptic events (PNEE). At the last contact, the postsurgical psychiatric complication of 16 patients (16%) had failed to remit, despite multiple pharmacological trials; four of these patients had developed a *de novo* postsurgical depressive disorder. Univariate analyses identified persistent seizures, presurgical psychiatric history and a left temporal seizure focus as predictors of postsurgical psychiatric complications. Multivariate regression models, however, identified a presurgical history of depression and a left-sided seizure focus as predictors of postsurgical psychiatric complications. Interestingly enough, having failed to obtain gainful employment after surgery was not found to be a predictor of postsurgical psychiatric complications.

Other authors have not found a left temporal seizure focus associated with postsurgical psychiatric complications, however. For example, in a study of 107 patients, 90 of whom underwent an ATL and 17 an ETL, and who had a postsurgical follow-up period of 1 year, Quigg *et al*. [13] found that preoperative depressive traits predicted worse postoperative scores on scales measuring symptoms of depression. Although the side of surgery did not predict worse postsurgical symptoms of depression, there was a trend for foci to be right sided. Findings for the ATL subgroup were similar to those of the overall sample. These authors concluded that patients undergoing epilepsy surgery in the right hemisphere, especially those with high presurgical depression-related morbidity, may be particularly susceptible to clinical depression.

Presurgical ictal fear or panic has also been associated with postsurgical psychiatric complications. For example, Kohler *et al*. [14] studied the association of ictal fear with mood and anxiety disorders before and 1 year after ATL in three groups of 20 patients: one with ictal fear, one with other types of auras and a third group with no auras. Evaluations of psychiatric disorders were carried out before surgery, at 1–2 months and 1 year after ATL. The majority of patients in the three groups experienced mood and anxiety disorders before surgery with similar frequencies. Mood and anxiety disorders declined in the two control groups, but not in the ictal fear group after surgery. Postoperative mood and anxiety disorders were more common in patients with persistent seizures and in those in the ictal fear group who were seizure free. Furthermore, a majority of patients with ictal fear required the use of psychotropic medication after surgery.

Presurgical postictal psychosis. Kanemoto *et al*. [15] identified an association between presurgical postictal psychotic episodes (PIPE) and postsurgical mood disorders in a study of 52 patients who underwent an ATL. Postsurgical mood disorders presented as manic and depressive episodes during the first two postsurgical years. In summary, postsurgical depressive and anxiety disorders are relatively common and a presurgical history of depression appears to be a predictor of this complication.

Postsurgical psychosis

The prevalence rates of postsurgical psychotic complications have been estimated to range between 1% and 10% among patients undergoing an ATL. Yet, data regarding postsurgical psychotic episodes are derived from smaller case series and studies that are fraught with serious methodological problems. For example, several case series have included a mixture of patients with presurgical and *de novo* postsurgical psychotic disorders.

De novo postsurgical psychotic episodes may present as schizophreniform-like disorders, manic episodes and postictal psychotic episodes. For example, Shaw *et al*. [16] identified 11 patients who developed *de novo* postsurgical schizophreniform psychosis among 320 consecutive patients (3.2%) who underwent an ATL. Psychotic symptomatology became apparent within the first year in all patients. These 11 patients were compared with a control group of 33 patients. Psychotic patients were more likely to have bilateral epileptiform activity, a smaller amygdala in the non-operated side and pathologies other than MTS. The study carried out at Rush Epilepsy Center cited above yielded

similar prevalence rates, as *de novo* psychotic episodes were identified in four patients within the first 6 months after an ATL, consisting of a manic episode in two and a paranoid episode in the other two patients [12]. Two of these patients had lesional epilepsy, caused by dysembryoplastic neuroepithelioma (DNET) in one and a ganglioglioma in the other. Symptoms remitted in two patients with pharmacotherapy without the need for hospitalization while the other two had to be hospitalized in a psychiatric unit. In one patient, symptoms remitted after the first admission, whereas the second patient had to be hospitalized twice.

In a study of 57 consecutive patients who underwent an ATL, Leinonen *et al*. [17] identified five (8.8%) who developed postoperative psychotic episodes. Two (3.5%) patients had experienced PIPE before surgery, which continued postsurgically. Among the other three patients, two (3.5%) experienced a definite *de novo* schizophreniform psychotic episode, and one patient (1.8%) met the criteria for a probable *de novo* psychotic episode. Among 74 patients who underwent an ATL, Jensen and Larsen [18] identified nine (12.1%) who developed a *de novo* psychotic disorder. Six out of these nine patients began experiencing psychotic symptoms after they became seizure free.

The risk of postsurgical psychotic episodes has been associated with right temporal seizure foci. For example, Mace and Trimble [19] reported seven consecutive patients who developed *de novo* psychotic episodes following an ATL, in six of whom it developed in the right temporal lobe: one developed a delusional depression, four developed a schizophrenic-like psychosis, and one patient was diagnosed with Capgras syndrome. Unfortunately, this relation has been suggested on the basis of these small case series and needs to be confirmed in larger multicentre studies.

The presence of gangliogliomas or DNET has also been associated with the development of *de novo* postsurgical psychotic disorders. Andermann *et al*. [20] reported six patients from four centres who experienced a *de novo* psychotic disorder [20]. The psychotic disorders consisted of schizophreniform-like episodes with paranoid and depressive symptomatology. These investigators estimated a risk of 2.5% for the development of *de novo* psychosis (1 in 39) in patients with this type of lesion who undergo an ATL.

Postsurgical manic episodes can also be psychiatric complications of ATL. For example, from a case series of 415 consecutive patients, Carran *et al*. [21] identified 16 patients (3.8%) who developed a *de novo* manic episode occurring within the first year after the ATL. These episodes were short-lived in all but one patient. Compared with a control group of asymptomatic patients matched for age and gender and a second group of 30 patients who experienced a postsurgical depression, patients with postsurgical mania were more likely to display bilateral electrographic abnormalities and to have a right temporal seizure focus, although this difference did not reach significance when compared with the depressed group. Postsurgical symptomatic patients were more likely to have experienced GTC seizures before surgery and to fail to achieve seizure freedom postsurgically.

Whether or not the development of *de novo* postsurgical psychotic episodes reflects a phenomenon of forced normalization has been the source of significant debate. For example, Stevens [22] identified a *de novo* psychotic disorder in two patients within the first 12 months after surgery from a group of 14 patients who had undergone an ATL and had been followed for a period of 20–30 years. Both patients were seizure free.

De novo postsurgical postictal psychotic episodes

Christodoulou *et al*. [23] reported three cases (1%) among 282 consecutive patients who had undergone an ATL. All three patients had seizures predominantly from the non-surgical side or had bilateral independent seizures; none of the patients who failed surgery but continued to have seizures only from the side of the surgery developed *de novo* PIPE. This supports the conclusion by other authors that patients with PIPE (chronic or *de novo*) have bilateral independent temporal lobe dysfunction [24]. Manchanda *et al*. [25] identified four patients (1.3%) who developed a *de novo* PIPE among a group of 298 consecutive patients who had undergone an ATL. All four patients had a right-sided resection and had no preoperative psychiatric history.

It has been established in several studies that patients with PIPE are at significantly greater risk of having bilateral independent ictal foci [24,26–28]. In a study completed at the Rush Epilepsy Center, the occurrence of PIPE predicted the presence of bilateral independent ictal foci with an 89% probability [24]. By the same token, patients with recurrent PIPE are at significant risk of developing interictal psychosis [29]. To minimize this risk, clinicians must carefully weigh the possibility of offering 'palliative' surgery to patients with PIPE and bilateral ictal foci, particularly those with mesial temporal sclerosis (MTS), provided that most seizures originate from the side of the MTS and the neuropsychological data are concordant with the intended surgical target.

Postsurgical psychogenic non-epileptic events

Ferguson and Rayport were the first authors to describe the occurrence of postsurgical *de novo* PNEE [30]. The prevalencerates of postsurgical PNEEs are relatively low, ranging between 1.8% and 10% among the different case series. For example, in the study carried out at the Rush Epilepsy Center cited above, 7% of the patients developed *de novo* PNEEs [12,31]. The development of a *de novo* postsurgical PNEE has been attributed to the 'stress' associated with a 'seizure-free' life in patients with chronic epilepsy who are not 'emotionally, physically or economically ready' to face their own or their families' increased expectations. Although this 'hypothesis' makes intuitive sense, the available data do not seem to support it. In the Rush Epilepsy Center study, a presurgical lifetime psychiatric history was significantly associated with the development of postictal PNEEs. Interestingly enough, PNEEs were not reported in seizure-free patients; in fact, persistent seizures were significantly associated with the development of *de novo* PNEEs. Furthermore, failure to obtain gainful employment was not associated with the development of PNEEs.

Ney *et al*. [32] identified *de novo* postsurgical PNEEs in 5 out of 96 patients who underwent epilepsy surgery over a period of 11 years [32]. A low full-scale IQ, preoperative psychiatric comorbidity and major surgical complications were identified as risk factors. Glosser *et al*. [33] identified 22 patients with postsurgical *de novo* PNEE corresponding to a prevalence rate just below 10%. Most of these patients were women with primary right hemisphere seizure foci and onset of their epileptic seizures after adolescence. In this study, preoperative psychiatric diagnoses

were not related to increased risk of PNEE. Reuber *et al.* [34] identified 13 patients with both epileptic seizures and PNEE and investigated their postsurgical outcome: 11 out of the 13 patients had significant clinical improvement postsurgically. However, in 2 out of 13 patients the severity of the PNEE (including pseudostatus epilepticus) increased postoperatively despite a significant improvement of their epileptic seizures. Both patients had a presurgical psychiatric history.

Postsurgical somatoform disorder

This type of psychiatric complication is either rare or underrecognized. To date there has been one case series of 10 patients who developed a somatoform disorder (other than PNEE) after ATL [35]. Seven of the 10 patients developed an undifferentiated somatoform disorder, one had pain and body dysmorphia, another had pain disorder and another had body dysmorphia alone. Somatoform disorder was significantly more common among patients who underwent a right ATL ($n = 9$).

Does epilepsy surgery have any impact on presurgical psychiatric disorders?

Anxiety and depressive disorders after anterotemporal lobectomy and extratemporal resections

Epilepsy surgery appears to facilitate the remission of psychiatric comorbidities at follow-up evaluations. In the study carried out at the Rush Epilepsy Center, a lifetime psychiatric history prior to surgery had been identified in 56 patients, of whom 51 were symptomatic at the time of the psychiatric evaluation [12]. At the last contact, 14 continued to be symptomatic despite multiple treatment strategies and an additional 14 patients were symptom free on psychotropic medication. Thus, epilepsy surgery resulted in total remission off psychotropic medication in 45% of the patients. Among the 44 patients reported by Glosser *et al.*, six (15%) were symptomatic before surgery and became asymptomatic postsurgically [11]. Twenty-one patients were unchanged in their psychiatric status: eight who were symptomatic and 13 who were asymptomatic before surgery. Although the overall prevalence of psychiatric disorders had not changed 6 months after surgery, the symptom severity measured with the Brief Psychiatric Rating Scale had improved significantly. In the study reported by Altshuler *et al.* [8], 17 out of 49 patients (35%) had a lifetime history of at least one major depressive episode. Eight of these patients never experienced another major depressive episode postsurgically. In this study, as in our study, the only predictor for postsurgical depressive disorder was a presurgical history of depression. Devinsky *et al.* [36] reported the results of a study of 360 patients from seven epilepsy centres in the USA who underwent epilepsy surgery; 89% had an ATL. Psychiatric syndromes were identified at baseline and 2 years after surgery with a structured interview, the Composite International Diagnostic Interview (CIDI). Presurgically, 75 patients (22%) met criteria for a diagnosis of depression, 59 (18%) of anxiety disorders and 12 (4%) of other psychiatric disorders, including bipolar illness and schizophrenia. At the 2-year postsurgical evaluation, only 26 patients (9%) met diagnostic criteria for depression and 20 (10%) for anxiety, and three patients (1%) met criteria for other psychiatric diagnoses. Thus, epilepsy surgery had resulted in symptom remission in more than 50% of patients. In this study, the presence of an anxiety or depressive disorder postsurgically was not associated with seizure outcome.

Psychotic disorders

The decision to consider epilepsy surgery in patients with refractory epilepsy and comorbid psychotic disorders continues to be the source of much controversy among epilepsy centres, as some exclude automatically these patients from consideration of epilepsy surgery, whereas others do not as long as the patient can cooperate during the presurgical evaluation and has a clear understanding of the therapeutic expectations and risks of the surgical procedure.

The impact of ATL on the postsurgical course of the psychotic disorder has varied from unchanged (in a majority of cases) to improved psychotic status and/or level of functioning. For example, in a study of 74 patients who underwent an ATL, Jensen and Larsen [18] identified 11 with a psychotic disorder *presurgically*. The surgical procedure had no impact on the psychotic disorders postsurgically. In a study of 52 patients, Kanemoto *et al.* [37] reported recurrence of psychosis in more than two-thirds of the patients with a preoperative history of interictal psychosis. Some of the patients (7 out of 12) remained with persistent psychotic symptoms for a long time [37]. In a series of five patients with a chronic psychotic disorder who underwent an ATL, Reutens *et al.* [38] reported an excellent seizure outcome in all patients. The surgical procedure did not modify the psychotic disorder postsurgically, but the absence of seizures facilitated their level of functioning. Marchetti *et al.* [39] reported six patients with presurgical interictal psychosis who underwent an ATL. Five out of the six patients achieved a seizure-free outcome and there was relative improvement in the psychotic disorder of five patients. These same authors reported an additional case of a 45-year-old female patient with a 30-year history of epilepsy and recurrent postictal psychotic episodes since the age of 35, which evolved to a chronic refractory interictal psychosis [40]. After having a right ATL she became seizure free, with remission of the psychotic disorder. All of these case series exemplify that patients with interictal psychosis can successfully complete a presurgical evaluation.

Impact of presurgical psychiatric history on postsurgical psychosocial outcome

Gainful employment

One of the obvious goals of epilepsy surgery is to facilitate gainful employment for unemployed patients or improve the type of job for those who have been able to maintain a job despite their pharmacoresistant epilepsy. Unfortunately, this is not always the case. A review of the literature identified the following variables as predictors of postsurgical employment: (1) reduction of seizures or seizure freedom; (2) presurgical cognitive ability; (3) absence of psychiatric comorbidity; (4) presurgical employment; and (5) improvement of neuropsychological function postsurgically [41]. In a study of 88 adult patients who underwent an

ATL at the Rush Epilepsy Center, the predictors of postsurgical gainful employment included working before surgery, achieving a seizure-free state, a negative lifetime history of depression and female gender [42]. Lendth *et al*. [43] found that a young age at the time of the surgery and improvement of the general neuropsychological functioning and especially attention are associated with employment after the surgery. In another study, Reeves *et al*. [44] found that being a student or working full time within a year before the surgery, driving after the surgery and obtaining further education after the surgery were associated with full-time work postoperatively. Clearly, a psychiatric evaluation is pivotal to identify patients who may have problems seeking and/or obtaining gainful employment.

Family dynamics

With the achievement of seizure freedom, patients have the expectations of becoming more independent, not only as it pertains to their ability to drive but in other areas of their life. Paradoxically, in some cases seizure freedom can have a negative impact on family dynamics. Indeed, some family members become accustomed to the patients' limitations and dependency on others and have difficulties allowing the patient to become more independent and see their role in life (unconsciously) as that of a 'care taker' without which they cannot 'function'. Unfortunately, these dysfunctional family dynamics are not rare in families of patients with a chronic illness like epilepsy, and invariably are bound to lead to conflict when patients try to become more independent. In fact, divorce is not an uncommon 'complication' of successful epilepsy surgery. By the same token, some patients who for a long period of time became too dependent on relatives feel unable to become more independent. Having a clear understanding by the epilepsy team of these family dynamics must be part of any presurgical evaluation and all couples and families need to be evaluated for the eventual risk of this type of family problem.

Impact of presurgical psychiatric illness on postsurgical seizure outcome

Clinicians do not typically associate psychiatric history with a postsurgical seizure outcome. Yet, in December 2000, Anhoury *et al*. [45] published a study of 121 patients who underwent an ATL; those with a lifetime psychiatric history exhibited a worse postsurgical seizure outcome than those without. Likewise, S. Koch-Stocher (Epilepsy Center, Bielefeld, Germany, unpublished data) investigated the postsurgical seizure outcome among 100 consecutive patients who underwent an ATL; 78 had a presurgical lifetime psychiatric history. Among patients without co-morbid psychiatric history, 89% were seizure free after surgery; however, this occurred in only 43% of patients with presurgical psychiatric history. Kanner *et al*. [12] used a logistic regression model to identify predictors of postsurgical seizure outcome in 100 consecutive patients who underwent an ATL and found that a lifetime history of depression and smaller resection of mesial temporal structures were the *sole* predictors of persistent auras in the absence of disabling seizures; a lifetime of psychiatric disorder was a predictor of failure to achieve freedom from disabling seizures. These data raise another question: *Is it possible that a psychiatric history, particularly depression, is an 'indicator' of a more severe form of epilepsy?*

Presurgical psychiatric protocols

Are epilepsy centres concerned about postsurgical psychiatric complications?

In the survey of 47 major epilepsy centres in North America cited in the introduction of this chapter, one question asked whether or not the epileptologists of the centre believe that psychiatric complications following ATL are frequent enough to warrant a presurgical psychiatric evaluation. The data indicated the absence of a consensus on this issue, as 21 centres (45%) considered it to be a problem and 26 (55%) did not.

Are psychiatric evaluations being routinely carried out in epilepsy centres?

Data from the survey revealed that only 10 centres (21%) routinely perform a psychiatric evaluation in *every* patient who is being considered for ATL. The lack of available psychiatric consultants is typically blamed for the failure to carry out psychiatric evaluations in all presurgical patients. Therefore, the survey enquired on the *availability* and *use* of psychiatrists in each centre. Among the 47 centres, only 12 (26%) had a psychiatrist in their epilepsy team. Consultations were provided by the hospital's psychiatry liaison and consultation service (LCS) in the other 35 centres: in 10 (21%) the *same* psychiatrist was always available to do the consultation, whereas in 24 (51%) consultations were carried out by *different* psychiatrists. In one centre, consultations were done by the residents but the attending did not see the patients in person.

The availability of an 'epilepsy team psychiatrist' appears to make a significant difference to the concern of postsurgical psychiatric evaluations in these centres. Thus, 75% of centres with an epilepsy team psychiatrist voiced a concern of frequent postsurgical psychiatric complications, although this was true in one-third of centres in which consultations were carried out by LCS psychiatrists. Of note, there was no difference among centres in which the same (30%) or different (33%) psychiatrists performed the evaluation. These data suggest that psychiatrists with special expertise in psychiatric aspects of epilepsy are more 'attuned' to potential postsurgical psychiatric complications. These data also raise the question of the quality of psychiatric evaluations performed by psychiatrists that lack special expertise in the psychiatric problems of epilepsy patients. In fact, 35 centres (75%) voiced concerns on the failure to obtain in-depth psychiatric evaluations.

It is rather common for centres that lack an epilepsy team psychiatrist to rely on neuropsychological evaluations to identify co-morbid psychopathology. For example, among the 24 centres that get psychiatric support from a different LCS psychiatrist, 23 (96%) based their decisions to order a psychiatric evaluation on the basis of the recommendations of a neuropsychologist or if the patient was known to have a psychiatric history, and this was also the case in 8 of the 10 centres (80%) which had the same LCS psychiatrist available. In contrast, only 4 out of the 12 centres (33%) with an epilepsy team psychiatrist relied on these criteria.

An important question is whether or not neuropsychological evaluations are adequate to identify patients at risk for postsurgical psychiatric complications. After all, most neuropsychological evaluations rely on screening instruments aimed at identifying *current* psychiatric symptoms occurring during the prior 1–4 weeks, depending on the instrument used; thus, these instruments are likely to fail to detect any past psychiatric history that may be in remission at the time of the presurgical evaluation and to capture the complexity of the co-morbid psychiatric disorders that are so common in these patients, as discussed in the previous sections. Indeed, only with a comprehensive psychiatric evaluation that investigates present and *lifetime* histories can clinicians have the necessary information to formulate a correct psychiatric diagnosis, recommend the appropriate treatment and make estimations on the risk for potential postsurgical psychiatric complications. Furthermore, family psychiatric history is one of the leading risk factors of mood, anxiety and ADHD. Unfortunately, these data are rarely investigated in a neuropsychological evaluation. In short, screening instruments do not identify the complexity of such psychiatric comorbidities.

Can epileptologists and neuropsychologists rely on a *patient's self-report* of past or concurrent psychiatric history?

The answer to this question is also 'no'! Indeed, it is a well-established fact that most frequent psychiatric co-morbidities in epilepsy patients (depression, anxiety and ADHD) are very often unrecognized by the treating epileptologist and that only severe forms of these disorders are reported by the patients to the physicians [46]. In addition, some patients may not volunteer information on a co-morbid psychiatric disorder out of misinterpretation of such disorders being 'a normal reaction' to a life with epilepsy, whereas others may hide such history out of fear that such history would disqualify them from consideration for epilepsy surgery. Failure to recognize chronic depressive disorders is illustrated in a study of 97 patients with partial epilepsy with a depressive disorder severe enough to warrant the consideration of pharmacotherapy; 60% had been symptomatic for more than 1 year before any treatment had been suggested [47]. Only one-third of the 97 patients had been treated within 6 months of the onset of their symptoms.

What is the reason behind the failure of most epilepsy programmes to incorporate a psychiatrist in their 'team'? After all, all programmes have one, or more than one, neuropsychologist. The answer is ironically rather simple: lack of financial resources on the part of hospital psychiatry departments to provide a full or part-time staff psychiatrist to a single service. Indeed, a careful analysis of the 12 epilepsy centres with an epilepsy team psychiatrist reveals that the epilepsy programmes pay for part of the salary of their psychiatrist. Thus, epilepsy centres that wish to have a psychiatrist in their team will have to budget a fraction of the psychiatrist's salary in their operating costs.

Suggested protocols

Clearly, the evidence presented in the previous sections suggests that patients who undergo epilepsy surgery are at risk for postsurgical psychiatric complications. Accordingly, presurgical psychiatric evaluations must seek to obtain the following:

- *lifetime* and *current* psychiatric history of mood, anxiety, attention deficit disorders and psychotic disorders, and to identify any evidence of a personality disorder;
- a detailed history of the temporal relation of psychiatric symptoms to seizure occurrence (i.e. to establish if all symptomatology was interictal or if it presented as preictal or postictal episodes solely or in addition to interictal disorders);
- a family psychiatric history, as a genetic predisposition is a pivotal factor in the development of mood, anxiety and attention deficit disorders, the most frequent psychiatric co-morbidities in these patients;
- an assessment of family dynamics and, specifically, the role played by each spouse with respect to the decision-making process in economic and family-related matters as well as an assessment of whether or not the patient's spouse is ready to adjust to a greater independence associated with a postsurgical seizure-free state;
- the patient's and family expectations of the epilepsy surgery, with respect to seizure outcome and changes in the patient's quality of life, employment and potential cognitive risks.

These data can be obtained in a psychiatric interview with the patient and close family members. The evaluation may take 1–3 h, depending on the complexity of the psychiatric history at hand and may require two or three sessions with the psychiatrist. A vocational assessment and the need for referral to a vocational rehabilitation programme should be part of the presurgical evaluation. This type of evaluation can be often obtained from the hospital rehabilitation therapists or from governmental agencies that work with disabled patients.

Presurgical evaluations in research

The data obtained in the survey presented above clearly indicate the need for systematic research on the incidence and types of postsurgical psychiatric complications, and the impact of presurgical risk factors on postsurgical psychiatric seizure and psychosocial outcomes. To that end, any methodologically sound study must include a structured psychiatric interview aimed at identifying lifetime DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, Text Revision) psychiatric syndromes and personality disorders. Various diagnostic interviews are available and can be administered by trained research assistants. It should be remembered, however, that these interviews were developed for patients with primary psychiatric disorders and not for patients with epilepsy with psychiatric co-morbidities. The limitations of using these instruments are not known at this time. Furthermore, structured interviews specifically developed for patients with epilepsy will need to be elaborated in the future.

The most frequently structured interviews include: (1) the Structured Clinical Interview for Axis I and II DSM-IV Disorders (DISC) [48]; (2) the Composite International Diagnostic Interview (CIDI) [49]; (3) the Schedule for Affective Disorders and Schizophrenia (SADS) [50]; (4) the Diagnostic Interview Schedule [51]; and (5) the Mini International Neuropsychiatric Inventory (MINI) [52].

It should be said that these psychiatric interviews need not be given in their entirety. Indeed, depending on the question to be addressed by the specific study, special sections of a questionnaire can be administered. For example, in the case of a study on mood

and anxiety disorders, investigators can decide to administer the section of these disorders of the SCID.

Structured interviews have been developed specifically for the identification of psychiatric syndromes in children and adolescents. The most rigorous is the SADS, adapted from the adult version [53]. We cannot emphasize enough the need to include an instrument that investigates the family psychiatric history. The Family History Screen for Epidemiologic Studies (FHE) is a user-friendly screening instrument that can be used in research [54].

Self-rating *screening* instruments are the favourite methods to acquire psychiatric data in research studies of epilepsy patients because of the logistical ease and low costs. Unfortunately, these instruments are designed to detect symptoms and not to establish a DSM-IV diagnosis, let alone the diagnosis of psychiatric entities with all their complexities and atypical manifestations encountered in patients with epilepsy. Thus, the sole use of these instruments represents the most frequent methodological error in psychiatric research studies in epilepsy. The argument for exclusively using screening instruments is that they have been validated to identify conditions such as MDE, some with acceptable levels of sensitivity and specificity, and the severity of the depressive episodes. Thus, proponents of the sole use of these scales might reason 'if a patient has a score of >30 on the Beck Depression Inventory-II, can it be anything other than an MDE?'. Although this statement is probably correct, an MDE may be the expression of more than one type of mood disorder, each with a different prognosis and treatment strategy (see section on depressive symptoms in this chapter).

As in the case of structured interviews, most of the screening instruments were developed for the screening of symptoms in patients with primary psychiatric disorders and not in patients with epilepsy. The only exception is the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [55] (see below). In addition, two screening instruments for the identification of symptoms of depression, the Beck Depression Inventory-II (BDI-II) and the Center for Epidemiologic Studies-Depression Scale (CES-D), have been recently validated in patients with epilepsy [56].

Clearly, the use of screening instruments for psychiatric research in epilepsy must be used *in conjunction* with a structured psychiatric interview designed to establish a DSM-IV-TR diagnosis; only then do these screening instruments yield meaningful data, as they permit regular rescreening to measure changes in severity of symptomatology. The most frequently used screening instruments in adults include the screening of general psychiatric, depressive, anxiety and obsessive–compulsive symptoms.

Screening of general psychiatric symptoms

The Adult Self-Report Inventories-4 are symptom inventories that can be used as a guide for conducting clinical interviews [57]. They include the behavioural symptoms of more than two dozen psychiatric disorders described in the DSM-IV. There are parallel versions of the Adult Self-Report Inventories that are designed to obtain information from both patients and significant others. These inventories take approximately 15–20 min to complete. Items are grouped according to diagnostic categories.

The Hopkins Symptom Checklist-90-Revised (SCL-90 R®) is used to evaluate a broad range of psychopathology. It consists of 90 items and can usually be completed in less than 30 min [58]. The scoring system includes nine symptom scales (somatization, obsessive–compulsive behaviour, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) and three global indexes. This scale has documented validity and has been in many treatment studies of mood disorders and schizophrenia.

The Minnesota Multiphasic Personality Inventory consists of a self-report personality inventory with 10 clinical scales (hypochondriasis, depression, hysteria, psychopathic deviance, male–female, paranoia, psychasthenia, schizophrenia, mania and social introversion) and three validity scales. The administration time is about 40–90 min [59].

Depressive symptoms

The Beck Depression Inventory-II (BDI-II) is the most commonly used self-rating scale for depression [60]. There are 21 items scored on a scale from 0 to 3 according to how the patient feels at the current time. The scale is sensitive to change and has been used in clinical drug trials. As stated above, the BDI-II has been recently tested in 205 patients with epilepsy from five epilepsy centres and was found to have a high sensitivity and specificity as a screening instrument of a major depressive episode [56].

The Center for Epidemiologic Studies-Depression Scale (CES-D) is a composite of 20 items, rated from 0 (rarely) to 4 (most or all of the time). It can yield scores from 0 to 60, with scores >16 being suggestive of depressive illness. This scale has also been recently validated for its use in patients with epilepsy [56].

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a new self-rating instrument that consists of only six items but which was *specifically* developed to screen for the presence of major depressive episodes in patients with epilepsy, while minimizing the risk of overlap with adverse antiepileptic drug effects or pre-existing cognitive problems [55]. Completing this instrument takes only 3 min or less and a score of >14 is suggestive of the presence of a major depressive episode.

Anxiety symptoms

The Hospital Anxiety and Depression Scale [61] is specifically developed for use in patients with a medical co-morbidity, and consists of seven-item self-rated subscales for both depression and anxiety.

The Beck Anxiety Inventory (BAI) [62] is a 21-item self-report measure of anxiety severity. The scale consists of 21 items, each describing a common symptom of anxiety over the past week on a 4-point scale ranging from 0 (not at all) to 3 (severely – 'I could barely stand it'). The items are summed to obtain a total score that can range from 0 to 63.

Goldberg's Depression and Anxiety Scales [63] consist of nine questions assessing mood and anxiety over the previous month; the full set of nine questions needs to be administered only if there are positive answers to the first four. The scales are devised specifically to be used by non-psychiatrists in clinical investigations. Scores are from 0 to 9.

The Hamilton Anxiety Rating Scale (HAM-A or HARS) [64] is a 14-item clinical interview scale (not self-reported) measuring somatic and psychic anxiety symptoms. The responses include five

degrees of severity ranging from 0 (none) to 4 (frequent and severe symptomatology). This instrument should be used with caution in patients with epilepsy, given the large number of somatic symptoms included in this scale which in patients with epilepsy can result from adverse effects of AEDs, potentially yielding false-positive suggestions of more severe anxiety symptomatology.

Obsessive–compulsive symptoms

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is the most widely used scale for rating obsessive–compulsive symptoms. It includes a symptom checklist as well as a 10-item scale that is rated by clinicians. It has been shown to be a highly reliable instrument that is sensitive for measuring changes in the severity of obsessive–compulsive symptoms [65].

Self-report measures for children and adolescents include the following.

- The Child Symptom Inventories (CSI-4) are screening instruments for the behavioural, affective, and cognitive symptoms of more than a dozen DSM-IV childhood disorders. There are Child Symptom Inventories for three different age groups: Early Childhood Inventory-4 (ages 3–5 years), Child Symptom Inventory-4 (ages 5–12 years) and Adolescent Symptom Inventory-4 (ages 12–18 years). There is a self-report measure for adolescent patients: Youth's Inventory-4 (ages 12–18 years) [66].
- The Child Behavior Checklist (CBCL), developed by Thomas M. Achenbach, is a scale that evaluates pathological behaviours and social competence in children from the ages of 4 to 16 years. Forms are available for teachers, parents and children. It is one of the most widely used scales for both clinical use and research [67].
- The Children's Depression Inventory (CDI) is a 27-item self-report questionnaire that can be given to 7- to 17-year-olds. It is currently one of the most widely used instruments for monitoring depression in children. Each question includes three statements of increasing severity [68].
- The Multidimensional Anxiety Scale for Children (MASC) is a scale for children and adolescents designed to assess symptoms of anxiety. The 39 items are scored on a scale from 0 to 3 as follows: 0 = never true about me; 1 = rarely true about me; 2 = sometimes true about me; 3 = often true about me [69].
- The Conners' Parent/Teacher Rating Scales identify behaviour problems through parent and teacher report and particularly symptoms of ADHD. It is available in three versions: a 93-item version, a 48-item version and a 10-item screening version. It is used in children ranging in age from 3 to 17 years [70].
- The Leyton Obsessional Inventory-Child Version (LOI-CV; Short Form) is a 20-item inventory, with 'yes/no' responses adapted from the adult version, to assess obsessive–compulsive symptoms [71].

Impediments for psychiatric evaluations

The second question of the survey enquired about the *availability* and *use* of psychiatrists in each centre. Among the 47 centres, only 12 (26%) had a psychiatrist in their epilepsy team. Consultations were provided by the hospital's psychiatry LCS in the other 35 centres: in 10 (21%) the *same* psychiatrist was always available to do the consultation, whereas in 24 (51%) consultations were carried out by *different* psychiatrists. In one centre, consultations were carried out by psychiatry residents who then staffed the cases with their staff psychiatrist.

Disclosure of postsurgical psychiatric complications

As shown above, epilepsy surgery is associated with postsurgical psychiatric complications which should be openly discussed with patients and family members with as much detail as the other surgical risks. Indeed, patients should be advised of the risk of postsurgical depressive and anxiety episodes occurring within the first 12 months, with a higher symptom incidence in the first 3–6 months and a tendency to remit by 12–24 months. This is especially true when the patient has a previous history of a mood disorder and the symptoms are actually an expression of a recurrence or exacerbation of presurgical depressive and/or anxiety disorders, whereas *de novo* mood/anxiety disorders are significantly less frequent. In patients undergoing ATL, *de novo* depressive and anxiety disorders can be expected in 10–15%, and a risk of 10–15% of persistent mood and anxiety disorders should be disclosed. Patients undergoing extratemporal resections have a lower risk of developing postsurgical psychiatric complications compared with patients undergoing an ATL, although the data available on postsurgical complications after ETL are rather sparse and more studies are needed to establish the actual risk. With respect to the potential risk of postsurgical psychotic complications, patients and family members should be advised that, although *de novo* postsurgical psychotic complications have been estimated to range between 1% and 10% following an ATL, the actual frequency remains to be established.

Conclusion

In summary, the evidence presented in this chapter is indicative of a high prevalence of psychiatric co-morbidity in epilepsy surgery candidates. This psychiatric co-morbidity, whether present at the time of the presurgical evaluation or preceding it, has significant implications in the patients' risks of postsurgical psychiatric complications, psychosocial adjustment as well as seizure outcome. Neuropsychological evaluations complement, but are not a substitute for, psychiatric evaluations.

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69 Mesial Temporal Lobe Surgery and Other Lobar Resections

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Introduction

Modern advances in epilepsy surgery have improved outcomes and reduced complications; however, surgery for epilepsy is not a new practice. As far back as the writings of Hippocrates, focal motor seizure onset was being used as a lateralizing sign for cranial surgery. In the 1500s, Duretus alleviated seizures related to a depressed skull fracture by elevating the impinging skull from the underlying brain [1]. The practice of removing brain tissue for the alleviation of seizures would wait for the late 19th century with the advent of effective anaesthesia techniques. Heyman was the first to report alleviation of seizures by the removal of a brain mass in 1831. The first series of cases involving resective brain surgery for seizures was published by Sir Victor Horsley in 1886 [1]. All of these early surgeries, and those in successive years, were based on pathological substrates with clear physical markers, such as post-traumatic lesions and infections. The surgical technique consisted of removing the lesion (lesionectomy) and sometimes removing the abnormal or damaged surrounding tissue as well.

The next advancement in epilepsy surgery came from the Montreal Neurological Institute, where Penfield and Jasper [1] recorded electrical activity from the brain during surgery under local anaesthesia. The goal was to define the extent of the epileptic zone based on abnormal electroencephalography tracings. This approach fundamentally changed the nature of the operation, from a procedure focused on a structural abnormality to one targeted by electrical pathophysiology. Grossly visible pathologies remained the target of many of the surgeries, but intraoperative electrocorticography (EcoG) was used to determine how far to extend the resection into the cortex surrounding a lesion. Also, for the first time, surgery for seizures with a cortical focus that was not grossly apparent on inspection was possible by directing the cortical resection to the electrophysiologically abnormal region. These procedures predated the advent of magnetic resonance imaging (MRI), which today would reveal some of the previously considered non-lesional seizure foci, and frequently abnormalities were found only postoperatively on pathological examination. Since the time of Penfield, several new modalities for localizing and delimiting the cortical focus of seizure activity for resection have been developed; however, the fundamental principle of using electrocorticography to delineate the margins of the region that should be surgically resected for seizure control remains the same today, albeit with some controversy.

Current practices of medial temporal lobe surgery

As more surgeries were performed based on abnormal electrophysiology and non-lesional cortical resections were performed based on the origin of epileptiform activity, it became clear that many of the non-lesional surgically remediable epilepsies of the temporal lobe represented a distinct pathology. A major advance over the last 20 years has been the identification of surgically remediable syndromes of epilepsy, the chief one being mesial temporal lobe epilepsy.

The original temporal lobe resections for non-lesional epilepsy originating in this area were quite extensive. The temporal lobe removal extended back from the anterior temporal pole for 7–8 cm (almost the entire length), included the medial temporal lobe structures of the hippocampus and amygdala and would sometimes be extended across the Sylvian fissure into the frontal lobe based on electrocorticography [2]. These resections proved fairly effective in controlling seizures, but they were associated with what would be considered unacceptably high morbidity by today's standards. Many of these patients were found to have complete hemianopsia, and there was an approximately 5% risk of hemiparesis or hemiplegia. Early epilepsy surgery programmes were associated with extensive research endeavours, including neuropathology research, that were trying to better elucidate the mechanisms underlying the unique temporal lobe epilepsy phenomenon. It became clear that these 'non-lesional' temporal lobe epilepsies commonly had abnormalities of the hippocampus with profound loss of neurones within the subfields. Pathological examination of surgical specimens from temporal lobectomy patients having electrophysiologically demonstrated medial temporal seizures made possible the determination that these pathological changes within the hippocampus were causing the seizures [3].

Concurrent with the determination of hippocampal sclerosis as an underlying epileptogenic pathology and the observation that removal of a sclerotic hippocampus alone frequently led to a seizure-free outcome, the sclerotic hippocampus became a lesion to be targeted in mesial temporal lobe epilepsy surgery. Early experiences made it clear that bilateral hippocampal pathology could not be addressed by resective surgery. The much studied

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patient, HM, developed complete and permanent anterograde amnesia following bilateral hippocampus removal [4]. However, targeting a unilateral sclerotic hippocampus made possible more limited temporal lobe resections that were safer than previous surgeries and led to fewer complications. Spencer *et al*. [5] developed a refined, standardized approach to resection of the medial temporal lobe structures that was more conservative in neocortical resection than previous approaches but proved highly effective in controlling seizures. In this approach, only the anterior lateral temporal lobe is resected, followed by entry into the temporal horn of the lateral ventricle, where the hippocampus is then identified and resected. Because of this, the extent of neocortical resection is standardized at 3–3.5 cm from the temporal tip, preserving the entire superior temporal gyrus [6]. This approach allows extensive resection of the hippocampus back to the tectal plate, an important detail given the findings of several studies that indicate there is a greater chance of seizure control as more hippocampus is removed but not with greater neocortical tissue resection in mesial temporal lobe epilepsy surgery [7,8].

Two other approaches to temporal lobe epilepsy surgery have been developed, one potentially more extensive and one more limited. The first of these was developed by Ojemann and colleagues [9,10] and included awake craniotomies with extensive intraoperative cortical mapping and electrocorticography. For temporal lobectomies, the final hippocampal and neocortical resection was tailored based on electrocorticography from the hippocampus and neocortex. Greater knowledge of the neocortical localization of language during surgery enabled more extensive resections based on electrocorticography [9,10]. Some patients with clear lesions in the temporal lobe neocortex also had a seizure focus in the hippocampus, suggesting dual pathology and requiring resection of both the neocortical lesion and the hippocampus for seizure control. It is thought that seizures from the neocortical focus may create a seizure focus in the hippocampus over time, possibly by promoting hippocampal sclerosis. A more limited approach to surgery for medial temporal sclerosis was initially developed in Europe and remains more popular with European neurosurgeons than those in the USA. The selective transcortical, transventricular amygdalohippocampectomy procedure was developed by Niemeyer [11] and further refined with an approach through the Sylvian fissure by Yaşargil [12]. For this approach, a small cortical incision is made through the superior temporal gyrus or by splitting the Sylvian fissure through the circular sulcus into the temporal horn of the lateral ventricle. Once in the ventricle, the hippocampus and part of the amygdala are removed, similar to the other temporal lobectomy procedures, but the temporal neocortex is left almost entirely intact, especially when the approach is transsylvian, although this approach does involve resection in the temporal stem. Amygdalohippocampectomy has demonstrated similar seizure-free outcome rates as the other types of temporal lobe surgeries [13] with some claims of less impairment on some neurocognitive measures, especially in the dominant temporal lobe [14,15]. However, the technique can be more technically challenging and has greater potential for disruption of the middle cerebral artery branches in the Sylvian fissure, possibly resulting in hemiparesis.

Medial temporal lobe resections are also performed for other lesions apart from the syndrome of mesial temporal or hippocampal sclerosis. A variety of neoplastic, vascular and other lesions can involve the medial temporal lobe, and their resection involves complex considerations regarding the risk inherent in the lesional pathology as well as the epileptogenicity of the lesion. These issues are discussed in a separate chapter devoted to lesional epilepsy.

Extratemporal resections and temporal lobe resections outside the medial temporal lobe

Medial temporal lobe surgery has evolved into a standard resection, albeit with some variations, based on the understanding of a fairly uniform pathology defining a surgically remediable syndrome. In contrast, surgical approaches to extratemporal lobar resections rely more on a process of delineation of the epileptogenic network, or 'focus', and do not follow a uniform surgical approach. When there is a lesion that is apparent through MRI, the approach is readily tailored to address the relationship of the lesion to the seizures, and then a surgical approach is developed, often aimed at removal of the lesion and, when appropriate, additional affected brain tissue presumed to be involved in the generation of seizures. Such lesions may be neoplastic, vascular, traumatic, infectious or related to developmental anomalies. Surgical approaches may range from strict lesionectomy to large-scale resection and even hemispherectomy or hemispherotomy for particular syndromes. These approaches are discussed in other chapters in this book.

Most challenging are the non-lesional extratemporal epilepsies, in which a structural substrate is not readily available. A variety of tools are employed in the process of delineating the epileptogenic network responsible for such epilepsies. These modalities include video-electroencephalography monitoring, magnetoencephalography (MEG) and extensive neurobehavioural testing. A variety of advanced and particularly sensitive MRI methods have been developed to reveal subtle brain changes that escape the standard MRI methods. These include magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI) and high-tesla (T) imaging with 3-T and stronger magnets. Methods of coupling electroencephalography to MRI have also been developed recently. In a substantial number of cases, these non-invasive methods may not be sufficient and may help only in focusing the work-up process on regions that will need further study using invasive recordings with subdural electrodes and/or parenchymal depth electrodes directed to specific brain targets. Intracranial electrodes are discussed in the section on intracranial studies.

In many extratemporal cases, the epileptogenic network can be localized to a particular lobe, and the surgical work-up and surgical approach then become more focused. In each lobe the existence of an epileptogenic network or focus may warrant special consideration regarding clinical semiology, the details of the work-up, and the surgical approach, taking into account both epileptogenic and functional considerations. Epileptogenic considerations may be based on seizure spread patterns that may vary according to location. For instance, epilepsy of parietal and occipital origin may spread quite fast to the medial temporal lobe and have a clinical and electroencephalographic profile similar to that

of mesial temporal lobe epilepsy. Functional considerations are of particular importance; for example, resection in the occipital lobe may entail very different neurological sequelae than resection in the posterior frontal cortex.

Frontal lobe surgery

The frontal lobe is the largest lobe of the brain, the majority of which is the association cortex or cortex involved in executive functions with significant bilateral representation; therefore, unilateral resection of epileptogenic foci in large areas of the frontal lobe may be feasible. However, there are some characteristics of the frontal lobe that may make surgical resection difficult or impossible. First, proportionate to the size of the frontal lobe, many of the frontal epileptic foci are diffuse and widespread, making it more difficult to achieve complete resection. In addition, the primary motor cortex and Broca's area on the dominant side are in the frontal lobe, making surgical resection unfeasible if these regions are involved. Second, frontal lobe seizure activity is known to spread ipsilaterally and to the contralateral side rapidly, making identification of the specific focus of onset difficult. Frontal lobe seizures can have several characteristic semiologies that may help localize the region of seizure onset [16]. Seizures originating in the primary motor cortex typically present with focal motor activity and may produce the Jacksonian march as they progress, with ipsilateral clonic activity spreading anatomically from the region of onset to involve the entire half of the body. Supplementary motor seizures are characterized by more complex motor activity, including the stereotypical 'fencer posturing' in which the patient's eyes and head deviate to the contralateral side and the contralateral arm is extended and elevated. The other characteristic frontal lobe semiology is a complex partial seizure that may involve motor automatisms such as bicycling of the legs. Although primary motor cortex is not a region in which resection of the seizure focus can occur without significant motor deficits, supplementary motor cortex can be the target of effective and safe resection. Resection of supplementary motor cortex may lead to a postoperative dense contralateral deficit, but this resolves within days or weeks, returning the patient to full motor strength in the affected limb, with little or no residual deficit [17].

Occipital lobe surgery

Occipital lobe epilepsy is typically characterized by visual or oculomotor signs and symptoms, including visual auras that can be complex in nature, transient visual loss, blinking and eye movements [16,18,19]. These seizures are complicated by rapid spread to adjacent lobes, including the parietal and temporal lobes. Rapid temporal lobe spread can make localization by semiology difficult, especially if the visual symptoms are subtle. The seizure can have the characteristics of the typical temporal complex partial seizure with a visual aura. This requires careful monitoring, frequently invasive with widespread electrode coverage, to determine the true location of seizure onset. Occipital lobe seizure foci can be resected, but often at the cost of a visual field deficit. The further the resection is from the primary visual cortex in the calcarine fissure, the less the impact on the visual field; therefore, careful delineation of the margins of the epileptogenic focus is very important.

Parietal lobe surgery

Parietal lobe epilepsy is more difficult to localize by semiology than other lobar epilepsies because of the subtlety or absence of symptoms [16,20]. Abnormal sensations and the sensation of vertigo have been described, but more than one-half of the patients with parietal lobe epilepsy have no symptoms referable to the lobe of seizure origin. As with occipital lobe seizures, parietal lobe seizures spread quickly to adjacent lobes, most commonly the frontal and temporal lobes. For this reason it is not uncommon that seizures with parietal lobe onset are thought to come from the frontal or temporal lobes based on semiology. Surgical resection of a parietal lobe seizure focus is not without effects. Most commonly, the patients will have sensory loss, especially loss of proprioception. Although this may seem fairly insignificant, loss of proprioception can lead to a lack of coordination that may hinder higher-level motor activities, including driving a vehicle. In addition, resection within the dominant parietal lobe can lead to Gerstmann's syndrome, characterized by agraphia, acalculia, an inability to distinguish right from left, and finger agnosia. Resections in the non-dominant parietal lobe may lead to significant deficits, such as contralateral neglect and impairment in spatial orientation and skills [21]. Symptoms that may seem fairly benign can be severely disabling to a person with certain cognitively demanding careers and may lead to job loss.

Multilobar resections

Epileptic networks are not limited by our somewhat arbitrary definitions of lobar anatomy and frequently will overlap lobar borders to involve more than one lobe. Because of this, multilobar resections of seizure foci are not uncommon. Examples include temporo-occipital resections, as well as temporal lobe resections that extend to the orbitofrontal region and parietotemporo-occipital (PTO) resections in some paediatric epilepsy cases such as infantile spasm [22]. However, seizure foci that overlap multiple lobes are more likely to be large and to involve cortical regions that cannot be resected because of their function, and therefore typically have a lower chance of achieving seizure control. This does not eliminate the consideration of surgical intervention in these cases, but it does necessitate more conservative estimates and expectations of seizure control outcomes when discussing surgery with prospective patients.

The remainder of the chapter is devoted to discussion of the work-up, efficacy and potential complications of temporal and other lobar resections for the control of epileptic seizures.

Epilepsy surgery evaluation

Whether for a temporal, extratemporal neocortical or a medial temporal lobe seizure focus, the work-up leading to epilepsy surgery is the same in principle: attempting to localize the epileptogenic network or focus. The goal of epilepsy surgery is to identify an anatomically defined region that once removed will result in the neutralization of the network and cessation of the seizures. This region may be fairly uniform for surgically remediable epilepsy syndromes, such as mesial temporal sclerosis (MTS), or lesional epilepsy associated with tumours, vascular and other lesions. However, for other cases with no apparent lesions,

individually tailored resections span a wide spectrum and require extensive work-up.

The current evaluation for modern epilepsy surgery begins with inpatient video-electroencephalography to determine the general lobar location of seizure onset and to rule out pseudoseizures and other cases that do not fall into the surgically remediable epilepsy syndromes. This stage involves not only the identification of electroencephalogram (EEG) correlates of seizure onset, but also an understanding of the seizure semiology that may sometimes provide a clear clue as to the lobe involved. Such clues may be an early motor event pointing to an origin in the rolandic region, or an early simple visual event in a particular place in the visual field, pointing to a specific occipital lobe as origin. The initial work-up also includes detailed MRI, including special fine cuts in the coronal plane to evaluate for hippocampal sclerosis or other cortical lesions that may account for the seizures [23,24]. Surface MR coils, stronger magnet scanners and various specialized MRI methods (see later section on other magnetic resonance methods) have been developed to detect subtle structural changes, such as those that can be seen in cortical dysplasia. MRI evidence of multilobar abnormalities or no MRI-detectable lesion are associated with poorer postoperative seizure outcome than focal MRI abnormalities limited to one lobe, emphasizing the importance of MRI lesion detection [25,26]. The goal of this first stage of epilepsy surgery evaluation is to limit the region of evaluation for the seizure focus. At this point, if the EEG corresponds to a lesion on the MRI, the patient may be a candidate for resection of the lesion, supplemented by resection of additional epileptogenic brain surrounding it (extended lesionectomy) [27]. This topic is discussed in detail in Chapter 71. This is also the approach for a patient with classic complex partial seizures and unilateral hippocampal changes on MRI, compatible with medial temporal sclerosis that corresponds with the side of temporal lobe seizure activity on video-EEG monitoring. Here the EEG and MRI findings will likely lead to one of the procedures described in the previous section for mesial temporal lobe epilepsy. When there is no MRI apparent lesion, extensive work-up is often required. A variety of diagnostic tools have been developed, some more recently.

Positron emission tomography

Interictal positron emission tomography (PET) scans can be useful in delineating the seizure focus, especially in seizures of medial temporal lobe origin [28,29]. The interictal PET scan shows an area of relative hypometabolism in the region of seizure onset. Ipsilateral medial, but not lateral, temporal lobe hypometabolism on interictal PET is predictive of better postoperative seizure-free outcome after temporal lobectomy [30]. However, a region of hypometabolism can be non-specific and may represent any lesion or abnormality of the cerebral cortex, whether epileptogenic or not. In addition, some epileptogenic pathologies such as post-traumatic gliosis will have hypometabolism throughout the abnormal region, masking the potential localizing properties of the study within the lesion. In conclusion, it is important to understand that the extent of the hypometabolic zone may be considerably larger than the epileptogenic zone; only the latter needs to be removed for control of the seizures.

Single photon emission computed tomography

Ictal single photon emission computed tomography (SPECT) is also useful for seizure onset localization in both medial temporal [31] and neocortical epilepsy, especially when co-registered to MRI (subtraction ictal SPECT co-registered to MRI, or SISCOM) [32]. The extent of resection of the cortical region identified as the seizure focus on the ictal SISCOM is correlated with the rate of seizure control [33]. Ictal SPECT can be more useful than interictal PET in determining seizure onset related to large cortical regions that demonstrate baseline hypometabolism throughout, such as regions of post-traumatic encephalomalacia. To obtain an ideal ictal SPECT scan, the radioisotope should be injected within 45 s of seizure onset [32]. Because of this, it is frequently performed as an inpatient study. The isotope is typically only good for 1 day, and must be administered by someone with appropriate radiation training and authorization. An effective ictal SPECT study requires a dedicated programme as well as set-up and maintenance costs that may be too great for the medium to small programme or hospital.

Other magnetic resonance methods: magnetic resonance spectroscopy, diffusion tensor imaging

Another use of the MRI scanner in the evaluation of the seizure patient is MRS. Postictal MRS shows increased signal from choline-containing compounds as well as creatine and phosphocreatine compounds and decreased signal from *N*-acetylaspartate in the seizure focus, and is effective in lateralizing the epileptic focus [34]. These changes represent dysfunction of neurones and glia rather than neuronal loss [35], demonstrated by their reversal in the contralateral hippocampus following medial temporal lobectomy [36]. The efficacy of MRS in guiding effective epilepsy surgery has not been established, and this imaging technique is not widely used clinically. MRI DTI, a technique used to evaluate the white matter tract projections in the brain, has been investigated as a potential imaging modality for determining seizure focus in non-lesional epilepsy syndromes. DTI has shown changes in both neocortical seizure foci [37,38] and hippocampal sclerosis [39] but does not yet have the reliability to be utilized clinically for determination of the seizure focus except in tuberous sclerosis, in which DTI was more accurate than structural MRI in localizing the epileptogenic cortex [40].

Magnetoencephalography or magnetic source imaging

Magnetoencephalography has been increasingly used in recent years as a tool in the presurgical evaluation of epilepsy patients. It is used mostly in the interictal state, but when it is used during a seizure it can provide useful ictal localizing information [41,42]. The MEG is based on the principle that electrical activities of groups of neurones within the brain create electromagnetic waves, the magnetic component of which can be detected and localized in three dimensions. This is especially useful when co-localized to the patient's MRI scan, resulting in what is termed 'magnetic source imaging' (MSI) [43]. MSI is most useful in neocortical epilepsy [44] and correlates with intracranial recordings in the majority of cases [45]. MEG is not as frequently used as other

studies because of its limited availability. The machine is highly specialized for studying brain magnetic activity and is expensive to purchase, install and staff. For reasons of cost and availability, MEG scanners are typically found associated with active brain research programmes and are most often utilized by affiliated epilepsy surgery programmes.

Functional magnetic resonance imaging

Functional MRI (fMRI) can be utilized to delineate the safety of resecting a seizure focus, especially in areas of motor and speech function [46], and when triggered by EEG spike activity it also holds promise for determining the seizure focus [47,48]. If the seizure focus is thought to be near or in motor or speech areas, the functional MRI will show the regions of the brain that have evidence of activation with movement or verbal tasks like word recognition or speech production. A reliable technique for determining memory function has not yet been developed, so functional MRI cannot currently be utilized in medial temporal seizure onset cases to determine if hippocampus resection will lead to memory deficits. For this, neuropsychological testing and the Wada test, are utilized. In addition, functional MRI shows all regions activated by a given function, but it does not demonstrate the necessity or sufficiency of any given area for the corresponding function. Therefore, it is not clear which of these areas, if inhibited or surgically removed, would lead to loss of function. To adequately investigate function in preparation for resection or disruption of one of these regions, a disruptive test through cortical stimulation is required, for example stimulation mapping using an implanted cortical electrode grid or intraoperative cortical stimulation mapping.

Studies of fMRI triggered by EEG spike activity have shown activity localized to the seizure focus in some patients [48] but not reliably. On EEG–fMRI, blood oxygen level-dependent (BOLD) effect corresponded to the spiking temporal lobe in the majority of temporal lobe epilepsy patients, but there was also activation in other brain regions, thought to represent activation of networks underlying the epileptic activity [49]. Because of the inconsistency in determining the seizure focus, this technology is not currently being used clinically but does show promise for future applications as it is further developed.

Neurocognitive evaluation

Neuropsychological testing can also be useful in preparation for and decision-making concerning epilepsy surgery. Traditionally, such testing has been especially useful in temporal lobe surgery. Material-specific memory deficits have been associated with unilateral hippocampal sclerosis. Although neuropsychological testing alone is not reliable for lateralization of the seizure focus [50] or predicting postoperative seizure outcome [51], it is useful in confirming localization and in determining the risks of surgery to memory function. A patient with good verbal memory function may be more at risk of significant memory deficits following dominant temporal lobe resection. The type of cognitive deficits present may also help in differentiating neocortical versus medial temporal lobe involvement, or a frontal versus temporal lobe focus.

'Wada test' in select cases

The intracarotid amytal test developed by Wada [52] originally for the lateralization of speech function by intracarotid amobarbital injection, has been more recently employed in lateralization of memory function [53]. The patient can be tested for various functions with one side of the brain anaesthetized by unilateral injection of sodium amobarbital into the intracarotid artery via a transfemoral catheter. The angio-Wada test is used particularly in preparation for a medial temporal lobe resection. For a patient to be a candidate for this type of epilepsy surgery, he or she should demonstrate little or no loss of memory function when the side of the proposed surgery is anaesthetized. Retrospective analysis of medial temporal lobe resections following the Wada test has shown that patients with superior memory performance from the non-epileptogenic side had better seizure-free outcomes, giving the Wada test some prognostic significance as well [54]. The Wada test has value in predicting learning and memory abilities in epilepsy patients with temporal lobe epilepsy, which is useful in the decision for surgery and presurgical counselling [53].

Intracranial studies

Once the non-invasive studies have been completed, a small percentage of patients proceed to an intracranial study with surgically implanted electrodes [55]. In these patients the various tests may have yielded non-concordant results, or insufficient information to enable focal resection. Intracranial monitoring is a hypothesis-driven technique used to identify a localized region of epileptogenesis once other non-invasive studies have been used to determine the general region or regions of the brain to be studied. Another potentially useful outcome of intracranial electrode implantation is the ability to use electrical stimulation to delineate brain function in or near regions that may need to be removed to control the seizures. Although helpful in outlining regions of the brain participating in functions such as movement and language, fMRI is limited to being used independently to determine safe regions for cortical resection. This limitation stems from the fact that the neural basis of fMRI BOLD signals is still poorly understood, and that the presence of BOLD changes with function do not mean that these regions are indispensable for the execution of these functions. Electrical stimulation mapping is still the 'gold standard' used to identify critical functions, and it often requires an awake, cooperative patient. Electrical stimulation can be performed either intraoperatively with patients awake or extraoperatively with implanted intracranial electrodes.

For patients suspected of having neocortical onset seizures, subdural cortical electrode grids are typically used to provide adequate coverage for determining the exact region of seizure onset and for stimulation mapping of functional areas such as speech, movement and sensation. Grid studies are typically augmented by cortical strip electrodes that can be extended under the edge of the craniotomy opening to rule out spread or a simultaneous seizure onset from another lobe unappreciated on scalp EEG.

Another type of intracranial electrode is the depth electrode, which is designed to penetrate brain parenchyma. Depth electrodes have the advantage of precisely sampling discrete targets in the brain, and monitoring seizure spread patterns in deep brain structures such as the hippocampus and amygdala [56].

However, depth electrodes do not provide extensive cortical coverage for mapping of seizure onset or function, so they are not as useful in planning resection of a neocortical focus. Intracranial electrode studies may provide valuable information leading to epilepsy surgery, even in patients with scalp EEG demonstrating bilateral seizure onset. A study of patients with bitemporal lobe onset on an EEG showed that the majority of the patients demonstrated onset only or predominantly from a single side and went on to surgery, with 40% being greatly improved and a 29% seizure-free rate [57]. In some cases, depth electrodes can show onset of seizures contralateral to what appeared to be the onset on scalp EEG [58]. This would suggest that medically intractable epilepsy patients, even if not having well-lateralized localization on scalp EEG, could be candidates for an intracranial electrode study.

Epilepsy surgery outcomes

Epilepsy surgery outcomes vary according to the location and pathology of the seizures. The primary goal of epilepsy surgery is to render patients seizure free. Complete seizure control is not always achieved, but postoperative seizure reduction is also used as a measure of success for patients with high preoperative seizure rate. An important factor affecting seizure control rate following epilepsy surgery is the location of the seizure onset; that is, the lobe involved influences the chance of achieving seizure control. This is partly due to the limitations imposed on the area of resection by the neurological function and anatomy of the lobe. Whereas cortical resection within the non-dominant temporal lobe can involve any or all areas of the lobe without loss of function, resection within certain areas of the frontal lobe could lead to motor deficits or aphasia, and resections within the occipital lobe would probably result in some degree of visual field deficit. Depending on the risk for neurological deficit, the surgeon may not be as generous in the resection of the seizure focus. In addition, medial temporal resection represents surgery that is fundamentally different from neocortical epilepsy surgery in that it encompasses a standardized approach based on the understanding of a well-defined syndrome and pathophysiology; therefore it may have a more favourable prognosis. The discussion of seizure outcomes will be organized based on location, with medial temporal lobectomy being discussed separately from the neocortical resection outcomes.

Medial temporal lobectomy has better reported postoperative seizure control rates than the other neocortical surgeries. Probably the most important paper in establishing the role of medial temporal lobe surgery in medically refractory epilepsy patients comes from a prospectively randomized study by Wiebe *et al*. [59]. Over a 1-year period the study found that 58% of the patients with temporal lobectomy were seizure free compared with only 8% of the patients receiving maximal medical therapy. The surgery group also had better mean quality of life and a higher percentage of them were employed or attending school at 1 year post surgery. Adverse events from surgery occurred in 10% of patients and represented problems such as memory difficulties (5%), but there were no mortalities; however, one patient in the medical group suffered sudden unexplained death from epilepsy (SUDEP). The authors of the paper recognized that the seizure-free rate from surgery was lower than in other large series of temporal lobectomy patients, but the study still demonstrated clear benefits of epilepsy surgery over medical management for medically refractory temporal lobe epilepsy.

Another prospective, randomized study evaluated the outcome of temporal lobectomy for seizure control in relation to the extent of hippocampal resection [8]. One group of 34 patients received the more limited hippocampectomy, extending only to the edge of the cerebral peduncle as part of the temporal lobectomy surgery. The other group of 36 patients received a more extensive hippocampal resection back to the superior colliculus. In this study, the patients with the more extensive hippocampal resection had better seizure control rates, with 69% of patients being seizure free compared with 38% being seizure free for the less extensive hippocampal resection. Interestingly, the two groups showed no difference in neuropsychological deficits, indicating that the neuropsychological effect of hippocampectomy is not dependent on the extent of the remaining hippocampal tissue. These findings suggest that patients who are at risk for neuropsychological deficit from hippocampal resection could suffer this deficit in any event. These studies strongly suggest that once the appropriate testing and preoperative evaluation has been performed to verify that the patient will not have a significant deficit from removal of the hippocampus, resection of the hippocampus should be extensive. Conversely, if there is concern about the patient having neurological deficits from hippocampal resection, the hippocampal resection should be avoided altogether, and the epilepsy surgery team should not gain false security about retaining hippocampal function by performing a more limited resection. These findings also agree with the findings of a retrospective analysis of the impact of the extent of temporal lobe resection on seizure outcome in temporal lobectomy patients based on volumetric analysis of postoperative MR images [7]. Overall, 68% of the patients were seizure free, with an average follow-up of 2 years and a minimum follow-up of 1 year. Only 17% of the patients with limited mesiobasal temporal resection were seizure free, whereas 76% of the patients with extensive mesiobasal temporal resection were seizure free. There was no difference in seizure outcome based on the degree of lateral temporal lobe resection. Again, this argues for an extensive medial temporal resection, including a complete hippocampectomy, but gives no support for more neocortical resection than necessary to provide access to the medial temporal structures.

Multicentre analyses of epilepsy surgery outcomes are also more objective and potentially more accurate sources of information about seizure outcomes of the various epilepsy surgeries. A meta-analysis of epilepsy surgeries was performed to determine seizure control outcomes for various surgery types [60]. In this meta-analysis, temporal lobe surgeries are listed as a group without separating out medial temporal resections from temporal neocortical resections. But the majority of temporal lobe epilepsy surgeries performed are medial temporal rather than neocortical, so this sample may be seen as mostly representing medial temporal lobe surgery outcomes. Analysis of 3895 patients in 40 studies showed a 66% seizure-free rate, with a confidence interval from 62% to 70%. In another set of studies of epilepsy surgery that were prospective and multicentre, medial temporal lobe resection surgeries

were analysed separately from neocortical resections. At 1 year, 77% of medial temporal lobectomy patients were seizure free [61]. However, at 2 years the proportion of patients who were seizure free had dropped to 68% [62]. These studies demonstrated both the high rate of seizure control with this surgery and also the low but present risk of relapse to active seizures over time.

Analysis of some of the larger series of medial temporal lobectomy cases may help elucidate some of the factors underlying the seizure-free rates. Analysis of 100 patients who had undergone standard anterior temporal lobectomy for complex partial seizures showed that 63% were seizure free by 2 years, at which point they stabilized and did not tend to have significant change in seizures in the following years [63]. Evaluation of 100 patients who had undergone the selective amygdalo–hippocampectomy demonstrated a 69% seizure-free rate at 1 year and a 58% seizure-free rate at 5 years, again showing a stability of seizure control at around 60% over time [12]. These similar studies using different surgical procedures had similar outcomes in seizure control, indicating equal efficacy of the two procedures. This was supported by a recent study directly comparing the two procedures in a retrospective fashion [13]. The authors of the study compared 50 patients who had cortical amygdalohippocampectomy with 50 patients who had selective amygdalohippocampectomy for intractable epilepsy with hippocampal sclerosis. At 1 year, 73% of the patients were seizure free, but by 5 years of follow-up the proportion of seizure-free patients had dropped to 49%. Most importantly, this study showed no statistically significant difference in seizure control rates between these two procedures, leaving the preference of procedure in the surgeon's hands based on technical complexity and training rather than efficacy.

Based on a review of the literature, the American Academy of Neurology published a practice parameter paper in collaboration with the American Epilepsy Society and the American Association of Neurological Surgeons on temporal lobe and other neocortical resections for medically intractable epilepsy [64]. Concerning temporal lobectomy surgery, their recommendations were largely based on the only class I evidence available, in the Wiebe *et al.* [59] paper discussed earlier in this chapter. In addition, they referenced 24 class IV evidence papers that supported the findings of the class I study. They cited the much higher rate of seizure-free outcome in the surgical group (64%) compared with the medical therapy-only group (8%) at 1 year, as well as the incidence of no surgical mortality and minimal surgical morbidity, when drawing their conclusions that the benefits of anteromesial temporal lobe resection are greater than continued treatment with antiepileptic medications in the medically intractable mesial temporal lobe epilepsy patient. Using the pooled data from the other 24 class IV studies, they found a 66.8% seizure-free rate with a 64–68% confidence interval (CI) and only 14% of patients (CI 12–16%) showing no reduction in their seizure frequency.

A definitive statement concerning extratemporal neocortical resection of a seizure focus could not be made in this practice parameter statement paper because of the lack of class I data within studies of these procedures. The conclusions of the paper are that further study of neocortical resections is necessary to determine if there is a benefit over continuation of medical therapy. However, within the paper, the results from the eight studies of neocortical resections were pooled to show a 49.7% seizure-free rate with a confidence interval of 44–55% [64]. In the six centres reporting patients without improvement, 20.5% (CI 16–25%) had no improvement of their seizure frequency. Given the limitations of these studies, they still show that after surgery approximately one-half of the patients became seizure free, a lower percentage than the medial temporal lobectomy patients but clinically significant nonetheless. However, potentially one-quarter of the patients undergoing neocortical resection do not benefit at all from their surgery. The multicentre study of epilepsy surgery had similar findings, reporting a 56% seizure-free rate after neocortical resection at 1-year follow-up [61] and 50% seizure free at 2-year follow-up, with 19% of the seizure-free patients relapsing after a 2-year period [62]. A recent paper examining the long-term results of 154 extratemporal lobe epilepsy surgery patients, the majority of whom were lesional with 5.8% non-lesional, found a low rate of relapse with 54.5% of patients seizure free at 1 year, 50.3% at 2 years, 52% at 5 years and 51.1% at 14 years [65].

The difficulty in performing standardized analysis of neocortical resections is the variability of outcomes depending on the lobe of resection in the existing retrospective studies. This is probably a result of the variability of neurological function represented in each individual lobe and the comfort level of the surgical team in committing a patient to a specific neurological deficit. Because of this, resections may be more conservative. Unlike medial temporal lobectomy, in which there is evidence that extending the hippocampal resection further posteriorly does not increase the impact on neuropsychological measures, extension of neocortical resection within the extratemporal lobes of the brain will lead to a further neurological deficit if large enough. A meta-analysis of epilepsy surgery outcomes analysed seizure-free rates in several different ways based on the included papers [66]. In the 25 papers that reported temporal and extratemporal resections grouped together, there was a 59% seizure free-rate, but in the two papers that grouped extratemporal resections, there was only a 34% seizure-free rate, showing the disparity of extratemporal versus temporal lobe resections. There were seven papers that looked at frontal lobe resections with a pooled seizure-free rate of 27% and one paper each looking at parietal and occipital lobe resections with 46% seizure-free rate in both. The authors attribute this difference to either the frontal lobe epileptogenic regions being larger and more difficult to completely remove in the largest lobe of the brain or the proximity to the motor regions in the posterior frontal lobe, limiting the feasibility of completely removing these lesions.

Few papers have analysed neocortical resections as a separate group for seizure-free outcomes. One study reports a seizure-free rate for temporal neocortical resections that surpasses the rate of medial temporal lobectomy outcomes, with 78% of patients being long-term seizure free [67]; however, many of these patients had neoplasms or other lesions that may have accounted for these excellent outcomes. This same study reported a 64% seizure-free rate from frontal neocortical resections; again this is probably higher than expected owing to the high number of patients with neoplasms and other lesions. The largest studies of outcomes from neocortical resections have come from the Montreal Neurological Institute. Analysis of 257 patients with frontal lobe resections for non-tumoral epilepsies with 2–49 years' follow-up showed a 26%

seizure-free rate [68]. This group also reported on a series of 79 parietal lobe epilepsy surgeries with a follow-up of 2–50 years [20] and a series of 37 occipital lobe epilepsy surgery outcomes [19] with a follow-up of 1–46 years, both of which had 46% seizure-free rates. One other study of 35 occipital lobe epilepsy surgery outcomes with a 1- to 14-year outcome showed a 46% seizure-free rate as well [18]. These results were represented in the meta-analysis [60] and demonstrate the disparity of outcome between medial temporal lobe resections and extratemporal neocortical resections.

The goal of epilepsy surgery is to make the patient seizure free, so it is appropriate to analyse and report seizure-free outcomes; but this does not tell the whole story about epilepsy surgery impact on patients. Important studies have been conducted to determine the impact of epilepsy surgery on patients' lives in a variety of areas in order to better understand the psychosocial and economic impact. Major surgery involves risk and can be disruptive to routine daily activities, so determining if patients have an overall improvement in quality of life after the surgery is important in assessing whether or not these surgeries are worthwhile. A meta-analysis of psychosocial outcomes from six controlled studies representing 509 medical and 799 surgical patients helps to answer these questions [66]. In five out of the six studies analysing seizure outcome, the surgical group did better than the medical group. In the four studies that looked at social outcomes, two found improvements in the surgical group compared with the medical group and two found the groups to be equivalent. Quality of life measures were improved for surgical patients compared with medical patients in two studies, and were found to be equivalent in one. Depression had a greater improvement in the surgical group than the medical group in the two studies that analysed this factor. Only one group looked at cognition and found that surgical patients did worse than the medical control subjects. Overall mortality was increased in the surgical group in one study but was equivalent to medical control subjects in two studies, probably owing to the low rate of mortality in epilepsy surgery and the risk of death from accidents and SUDEP that can be seen in patients with uncontrolled epilepsy. Although not universally positive, taken together, these results suggest that surgery is more beneficial for refractory epilepsy than the continuation of medical therapy in terms of the psychosocial aspects, with little to no increase in mortality compared with medical therapy, but some evidence of negative impact on cognition that should be accounted for in the decision-making process.

Several papers from the Multicenter Study of Epilepsy Surgery, a prospective observational cohort study, have addressed psychosocial factors. Among 396 patients who had epilepsy surgery, 75.5% said that they would undergo surgery again and 79.1% reported a strong overall impact of surgery on their lives at 2 years; however, only 7% of the patients had improvement in their employment status [69]. Postoperatively, both depression and anxiety levels were decreased at 3, 12 and 24 months after epilepsy surgery in 360 evaluated patients [70]. In both of these studies, patients who were seizure free had much better outcomes than those who continued to have some seizures. In a subset of 68 patients receiving temporal lobe epilepsy surgery, health-care costs were significantly decreased in the 2 years after surgery compared with the 2 years before surgery for those who were seizure free, but there was no difference for those with persisting seizures [71]. These results demonstrate clear patient benefits of epilepsy surgery, but only if the surgery results in a seizure-free outcome.

Epilepsy surgery complications

Epilepsy surgery is not without potential risks, and quantifying those risks is useful in combination with outcome data in counselling patients and assisting them in their decision-making concerning surgery. The epilepsy surgery programme at the University of Bonn in Germany has presented the rate of complications in 429 consecutive surgeries over a 6.5-year period [72]. These surgeries included temporal and extratemporal lobe resections as well as electrode implantations, callosotomies and hemispherectomies. The complications were divided into categories of surgical complications and neurological complications. Overall, there were 7.7% transient surgical complications and 0.7% permanent complications (hydrocephalus in all three permanent cases), and there were 3.0% transient and 2.3% permanent neurological complications. There were no mortalities reported. The most common surgical complications were wound infection at 3.5%, meningitis at 1.4% and deep vein thrombosis at 0.9%. The most common neurological complications were hemi- or tetraparesis at 2.3%, third-nerve palsy at 0.9%, and hemianopsia and dysphasia each at 0.7%. Separate analysis of annual complication rates over the 6-year period showed that surgical complications dropped from 13.2% to 3.7%, with wound infections decreasing from 13.2% to 0%, and neurological complications dropped from 10.5% to 3.7%, with hemi- or tetraparesis decreasing from 5.3% to 0.9%. These statistics show that epilepsy surgery has relatively low risks that are more often transient than permanent, and there is some evidence that risk is mitigated by the level of experience of the epilepsy surgery centre. The practice parameter paper from the American Academy of Neurology discussed the complications reported from seven institutions they reviewed, including mainly temporal lobectomies but also extratemporal resections [64]. From a total of 556 patients, there were only two non-operative deaths, one of which was from a trauma, making the overall procedure-related mortality 0.2%. Six per cent of patients had new neurological deficits including mild aphasias, third- or fourth-nerve palsies, visual field deficits greater than a quadrant, and hemiparesis (2% of patients). One-half of these deficits resolved within 3 months, making the risk of permanent neurological deficit 3%. The most common non-neurological surgical complication by far was postoperative infection, which occurred in 5% of patients.

For epilepsy surgery, each targeted lobe has the potential not only for general surgical complications but also for specific complications related to the neurological functions contained within the lobe and the surrounding anatomy. The randomized, prospective, controlled study comparing temporal lobectomy surgery with best medical management is helpful in establishing the complications specific to the surgery rather than the general complications associated with epilepsy [59]. There were no mortalities within the surgical group, whereas there was one sudden unexplained death in the medical group, emphasizing that epilepsy is

not a benign disease, having its own mortality rate, and that the choice not to proceed with surgery may not necessarily be the safest choice. Four out of the 40 surgery patients had adverse effects including a thalamic infarct causing sensory abnormalities, a wound infection, and two declines in verbal memory. Fifty-five per cent of patients had an expected superior quadrantanopsia as a side-effect of surgery. Depression (18% surgical, 20% medical) and transient psychosis (one patient in each group) occurred in both groups to a similar degree. In the study of corticalamygdalohippocampectomy versus selective amygdalohippocampectomy there were also no operative deaths among the 100 patients studied, and there was only a 4% complication rate, most of which were non-neurological surgical complications [13].

A study of 154 extratemporal, neocortical epilepsy surgeries found a higher rate of complications than seen in the temporal lobectomy studies [65]. There were no mortalities, but there were complications in 8.4% of the patients, with 1.9% having persistent paresis, 3.9% having visual field deficits, 0.6% having a subdural haematoma requiring surgery, and 1.9% with bone infections. In addition, 5.8% had transient neurological deficits that had no long-term impact. In a study of 126 neocortical frontal and temporal lobe epilepsy surgeries there were also no mortalities [67]. Five per cent of patients had surgical complications including meningitis, wound infections, pulmonary embolism and diabetic coma, and 4.5% had neurological complications including dysphasia, hemiparesis, brachial monoparesis and hemihypaesthesia, but all of these complications were temporary and were eventually fully resolved. In a study of 82 patients having parietal lobe resections for epilepsy there was a 52% complication rate with no mortalities; however, the permanent neurological deficit rate was 24% [20]. The permanent neurological deficits included contralateral cortical sensory loss, dysphasia, acalculia, anomia, agraphia, partial auditory and verbal agnosia, contralateral weakness, and disturbances of body image causing apraxia of dressing, hemi-inattention or neglect and contralateral visuospatial defects. Postoperative neurological deficits were also listed in one of the series of occipital lobe epilepsy surgeries, but given the location of the resections, visual field deficits were seen as side-effects of the surgery rather than complications [19]. There were two mortalities among these 42 patients. Fifty-nine per cent of the patients had preoperative visual field deficits. Postoperatively there was a 76% complete homonymous hemianopsia rate, transient aphasia in 4.8% and aseptic meningitis in 7.1%. Clearly, extratemporal lobe epilepsy surgeries have greater side-effects and risks of complications than temporal lobectomies.

Another concern specifically with medial temporal lobectomy is the impact of the surgery on the neurocognitive and language functions. In a retrospective analysis of 47 right-handed patients who underwent left temporal lobectomy for refractory temporal lobe epilepsy, the extent of medial and lateral resection was found not to influence neurocognitive outcomes [73]. These are the patients who would be expected to have the most significant cognitive impacts from surgery because the surgical target was the dominant temporal lobe responsible for verbal learning and memory. Average Wechsler Adult Intelligence Scale scores showed improvements in visuospatial reasoning for all resection types, but verbal reasoning was decreased in two out of the four resection groups. In addition, all groups showed decreases in the memory quotient on the Wechsler Memory Scale and decreases in all measures on the Auditory–Verbal Learning Test. However, a Wada test memory score in the ipsilateral hemisphere can be somewhat predictive of postoperative memory deficits, such that patients with high memory potential are more likely to have postoperative memory deficits [53]. In a randomized, prospective study of limited versus extensive hippocampal resection in medial temporal lobectomy, extent of tissue removal did not influence memory outcome, but left temporal lobectomy without signs of hippocampal sclerosis was associated with a decline in verbal memory, probably because the hippocampus removed was not only anatomically and pathologically normal but was functioning normally as well [8]. A study of verbal function following medial temporal lobectomy of dominant and non-dominant temporal lobes found no overall decrement in language functions in either group [74]. These surgeries were performed with conservative neocortical resection to minimize language impact. Thus, language function can be safely maintained following medial temporal lobectomy provided there is conservative neocortical resection, whether in the dominant or non-dominant temporal lobe.

Conclusion

Temporal lobe and other lobar surgeries for epilepsy have a long history, are well established and have shown better seizure outcome and decreased complication rates over time and with more experience in epilepsy centres. Improved surgical procedures, advances in techniques for preoperative localization of the seizure focus, as well as better understanding of the pathophysiology of distinct surgically remediable syndromes of epilepsy, are responsible for the increasing success of epilepsy surgery over the years. With low risk to the patient and class I evidence of high efficacy in eliminating seizures, with seizure-free rates ranging from 58% to 77%, temporal lobectomy for medial temporal lobe epilepsy represents a good option for the appropriate medically refractory epilepsy patient, a conclusion shared by the American Academy of Neurology in a practice parameter paper [64]. Extratemporal epilepsy or epilepsy involving the lateral structures in the temporal lobe may harbour a favourable surgical prognosis if an apparent lesion is shown by MRI. Neocortical resections for epilepsy, in the absence of structural lesions, are also effective in eliminating seizures in some patients, although less effective than temporal lobectomy or focal lesion-centred resections. However, the difficulty in localization of seizure onset, the functional constraints on resections and lack of class I evidence makes these surgeries a clinical option for medically refractory epilepsy that should be carefully considered on an individual patient basis, although deserving of a full evaluation by a qualified epilepsy surgery centre.

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70 Resective Surgery of Neoplasms

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Introduction

The association of brain tumour with epilepsy has been suspected since ancient times [1]. The occurrence of seizures and epilepsy in the presence of primary brain tumours has been observed for over a century [1–6]. Seizures are the most common presenting symptom in patients with slow-growing or well-differentiated low-grade tumours. Seizures occur in approximately 50% of patients with intracerebral neoplasms [5,6]. There is a direct correlation between the chronicity of the growth of the neoplasm and the incidence of seizures. In the Montreal series of 230 patients with tumours of the central nervous system, the majority were gliomas. Seizures occurred in 70% of patients with astrocytomas, in 92% of patients with oligodendrogliomas and in 37% of patients with glioblastomas [5,6].

In the classic book of William Gowers [2], published in 1881, a clear distinction between focal seizures due to a demonstrable pathological lesion and generalized seizures, constituting idiopathic epilepsies, was emphasized. However, Hughlings Jackson [3] was the first to provide a comprehensive understanding of the significance of focal seizures when he described uncinate seizures in patients with neoplastic and non-neoplastic lesions of the temporal lobe. He emphasized that epilepsy could be the initial and only clinical manifestation of a brain tumour [3]. Victor Horsley [4] reported his three landmark cases in which he surgically cured the patients of their focal epilepsy. More recently, various seizure patterns in patients with structural lesions and their surgical management were described by Penfield and Jasper [7], Spencer *et al.* [8], Boon *et al.* [9], Awad *et al.* [10] and Cascino *et al.* [11].

The remarkable development of neuroimaging during the past 20 years has allowed detection of various types of intracranial abnormalities in patients with medically intractable epilepsy with increasing frequency [8–11]. Primary brain tumours, hamartomas and vascular malformations are the underlying pathology in approximately 20–30% of patients with intractable epilepsy. Magnetic resonance imaging (MRI) is the most sensitive and specific imaging modality to distinguish a mass lesion from other pathological entities in patients with epilepsy [11–13]. If a circumscribed lesion is responsible for intractable seizures and the relationship of the lesion to the seizures can be verified, surgical resection of the lesion and surrounding brain tissue can render the patient seizure free and improve the quality of life [8–13].

With accumulating experience, it has become evident that the neurological examination, electrophysiological studies, seizure types and response to antiepileptic medications may not be useful in predicting the nature of the underlying pathology. Longstanding partial epilepsy may be related to an indolent low-grade glioma with a clinical course indistinguishable from that of a non-neoplastic process. Lesional epilepsy can be associated with simple partial seizures, complex partial seizures or secondary generalized tonic–clonic seizures. It is the purpose of this chapter to elaborate on the current concepts concerning the diagnosis and surgical management of patients with epilepsy associated with neoplastic mass lesions. The lesion associated with epilepsy may warrant neurosurgical intervention because of the mass effect, growth or haemorrhage. In other cases, the lesions are static and benign with the neurosurgical significance being related to the intractable epilepsy only; it is this latter group that is the subject of discussion in this chapter. The results of surgical resection of the lesion with respect to seizure frequency, surgical morbidity and psychosocial outcome will be discussed. Seizures specifically associated with cortical dysplasias and vascular and infective lesions are discussed elsewhere in this textbook.

Partial or localization-related epilepsy

Partial or localization-related epilepsy is the most common seizure disorder in the adult patient, and the most frequently occurring seizure type is a complex partial seizure (CPS) [14–17]. Approximately 45% of patients with partial epilepsy will experience medically refractory seizures that are physically and socially disabling [14,16]. A minority of patients who fail to respond to first-line antiepileptic drug (AED) therapy will be rendered seizure free with newer medical treatments introduced in the past decade [14–16]. Epilepsy surgery is an effective alternative form of therapy for selected patients with intractable partial epilepsy [18–26]. Patients with mesial temporal lobe epilepsy and lesional epilepsy may be favourable candidates for epilepsy surgery and have a surgically remediable epileptic syndrome [19]. The majority of these patients experience a significant reduction in seizure tendency following surgical ablation of the epileptic brain tissue [18–26]. The hallmark pathology of mesial temporal lobe epilepsy is mesial temporal sclerosis (MTS) [27,28]. The surgically excised hippocampus in these patients almost invariably shows focal cell loss and gliosis [27,28]. Patients with lesional epilepsy may have a primary brain tumour, vascular anomaly or a malformation of cortical development (MCD) [10,11]. The common

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primary brain tumours encountered in patients with partial epilepsy include a low-grade glioma, ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET), and a mixed tumour with features indicating both a neoplasia and an MCD [29–42]. Individuals may also have dual pathology with MTS co-existing with the lesional pathology. Patients with primary intraparenchymal neoplasms almost invariably have an abnormal structural MRI study [10,11]. MRI in these individuals may detect a specific intra-axial structural abnormality that may suggest the likely site of seizure onset and the surgical pathology [10,11]. MRI has a pivotal role in the selection and evaluation of patients for alternative forms of therapy [22]. The rationale for the presurgical evaluation is to identify the site of ictal onset and initial seizure propagation, i.e. epileptogenic zone, and determine the likely pathological findings underlying the epileptic brain tissue [24,43]. In patients with an MRI-identified foreign tissue lesion or unilateral mesial temporal sclerosis, the purpose of the electroclinical correlation is essentially to confirm the epileptogenicity of the structural abnormality [10,11]. The demonstration of concordance between the pathological substrate and the ictal onset zone indicates a highly favourable operative outcome in selected individuals.

Mechanism of epileptogenesis associated with structural mass lesions

The mechanism(s) of epileptogenesis associated with brain tumours is unknown [44]. Hughlings Jackson [3] observed that the pathogenesis of epilepsy in patients with tumours was related to the presence of a slow-growing tumour in the grey matter and the 'sudden excessive and temporary discharge of nerve cells', producing seizure activity [44]. Penfield [44,47] suggested that impaired vascularization of the surrounding cerebral cortex may produce hypoxic–ischaemic neuronal changes. Direct 'irritation' of the cortex by a tumour has also been proposed as the aetiology of seizure activity. In the symptomatic partial epilepsies, a focal structural abnormality is intimately associated with the epileptogenic area, the site of seizure onset [43]. Specific morphological neuronal alterations related to a focal brain lesion, for example tumours, have been observed that are potentially epileptogenic. The pathophysiological mechanisms of ictogenesis associated with intracranial mass lesions are poorly understood. Early proposed mechanisms included impaired vascularization of the surrounding cerebral cortex and direct irritation of the brain and denervation hypersensitivity due to partial isolation and transection of a region of the cerebral cortex [45,46]. There is conflicting evidence regarding the contribution of hereditary predisposition in the development of epilepsy in patients with intracranial structural lesions [9].

The mechanisms of epileptogenesis for different pathological lesions must vary as some are extracerebral and others are intracerebral, some tumours are infiltrative into the brain and others distort it by mass effect. This suggests that the aetiology of seizures in various lesional pathologies is multifactorial involving factors intrinsic to the lesion itself, the location of the tumour and factors unique to the host harbouring the pathology.

Factors unique to a pathological lesion, particularly tumours, may be associated with the expression of various ion channels and receptors, and the relative proportion of different cell types within the tumour. Amino acid disturbances, local metabolic imbalances, cerebral oedema, pH abnormalities, morphological changes in the neuropil, changes in neuronal and glial enzyme and protein expression and immunological activity are all thought to contribute to the pathogenesis of lesional epilepsy syndromes. Future studies from pathological specimens and the development of animal models may further characterize the relative contributions of each of these factors in the development of lesional epilepsy syndromes [28,48–53]. In addition to properties of the tumours themselves, numerous studies have investigated the role of various properties of peritumoral tissue [53]. These investigations have focused on how tumours located in the brain disrupt signal processing. It has been proposed that the tumour either infiltrates into brain tissue or exerts a mass effect, and so transects inhibitory populations of neurones; this upsets the balance of excitatory and inhibitory output in favour of overstimulation, resulting in seizures. In defining the area of resective surgery, Rasmussen [18] identified a primary localization, which is the site of seizure initiation, and a secondary localization, which indicates the volume of tissue adjacent to the site of origin that must be recruited to produce a clinical seizure. The amygdala and hippocampus appear to be critical sites of secondary localization by providing synchronized output and amplifying an ictal discharge [54,55]. Seizures originating as far posteriorly as the occipital lobe may preferentially spread forward through the hippocampus [56]. Anterior temporal lobectomy can result in seizure relief despite the presence of a posteriorly located temporal lobe tumour [57–59]. This suggests that the effect of surgery depends not on the excision of the primary epileptogenic focus, but on the elimination of the recruitment of other cells for full seizure development and interruption of the neuronal pathways required for seizure propagation. Histological studies have demonstrated gliosis or sclerosis of the mesial temporal structures in patients with medically resistant complex partial seizures and small vascular or neoplastic lesions in more posterior parts of the temporal lobe [60–64]. However, in 216 consecutive surgical specimens from patients with chronic, medically intractable temporal lobe epilepsy (TLE), Ammon's horn sclerosis was significantly more common in patients without focal mass lesions than those with focal lesions [49]. Dual pathology, if present, may produce a combination of neocortical and temporolimbic epilepsies (TLME) that necessitate a precise definition of the true epileptogenic area(s) in order to achieve maximum benefit from surgery [65].

Pathology: neoplastic lesions

Seizures occur in approximately 50% of patients with intracerebral neoplasms [6,18]. The incidence of seizures among patients with primary brain tumour is related to the tumour pathology and cortical localization (Table 70.1) [47,66]. Slow-growing, low-grade and well-differentiated gliomas are the most epileptogenic

Table 70.1 Primary brain neoplasms associated with seizures.

	Main characteristics	Neuroimaging characteristics
Pleomorphic xanthoastrocytoma (PXA)	Rare, but common in the epilepsy population Seen in the first three decades of life Two-thirds of cases occur in patients under the age of 18 years Most patients have a long history of seizures	Preferentially involves the peripheral temporal lobes Leptomeningeal attachment or adhesion is common with a base at the meninges and is seen in over 70% of cases Cysts form in one-third to one-half of cases Discrete mural nodule is often seen abutting the meninges Calcification is unusual Mural nodule often enhances May remodel overlying skull
Ganglioglioma	Contain both neuronal and glial elements Rare, accounting for 0.5–1% of all central nervous system neoplasms Common in the epilepsy population Overall 60–80% occur in patients under the age of 30 years Most are symptomatic in the second decade Chronic seizures are the most common symptom Epilepsy is resistant to medication 90% of the time	Most commonly involve the temporal lobe Cyst formation occurs in 38–50% of patients Often associated with a mural nodule Calcifications occur in 30% of cases Surrounding oedema is minimal Enhancement pattern varies from none to striking When peripheral, often associated with bony remodelling of the skull Can be associated with focal cortical dysplasia
Dysembryoplastic neuroepithelial tumour (DNET)	Rare, but common in the epilepsy population Often present in the second and third decades of life Male to female ratio 1 : 1 Usually cause seizures that can be refractory	Most commonly found in the temporal lobes Often wedge-shaped, cortical mass with multiple cysts May extend towards the ventricle Calcification in 20–36% of cases Usually no surrounding oedema Usually no enhancement May remodel overlying bone Over 50% are accompanied by focal cortical dysplasia
Oligodendroglioma	Uncommon, constituting 5–10% of gliomas Minority of tumours are anaplastic Generally occur in the fifth and sixth decades of life Male to female ratio 2 : 1 Most common symptom is seizure owing to cortical involvement	Strong predilection for subcortical white matter in the frontal and temporal lobes Heterogeneous hemispheric mass Foci of cystic degeneration are relatively common, but haemorrhage and necrosis are less frequent Calcification occurs in 70–90% of cases Enhancement pattern can be mild to moderate and inhomogeneous Remodelling of overlying skull can be seen
Low-grade fibrillary astrocytoma	Occur less frequently than high-grade lesions Uncommon with true incidence difficult to determine secondary to sampling and grading variability Represent 10–15% of gliomas Often occur between 20 and 40 years of age Seizures are a common presenting symptom	Focal or diffuse mass May have cystic degeneration, although necrosis/haemorrhage/oedema rare Calcification occurs in 15–20% of cases Enhancement can be absent or mild Erosion of the adjacent skull may occur
Pilocytic astrocytoma	Occur less frequently than high-grade lesions Represent 5–10% of gliomas Often occur in children or young adults with cerebral forms having a peak incidence at age 20 years Seizures are a common presenting symptom	Characteristically located around third and fourth ventricles, though can occur in cerebral hemispheres Solid or cystic mass Calcification occurs in 10% of cases Variable surrounding oedema Enhancement pattern varies

lesions (see Figs 70.1–70.6) [47,66]. In the Montreal series of 230 patients with gliomas, seizures occurred in 70% of those with astrocytomas, in 92% of those with oligodendrogliomas and in 37% of those with glioblastomas [47]. The incidence of epilepsy is lower in patients with glioblastoma, perhaps because of the shorter duration of the disease. These more aggressive lesions, including cerebral metastasis, are associated with a risk of seizures in the range of 20–30% [47].

Tumours located in close proximity to the centrotemporo-parietal region are more frequently associated with epilepsy [18,47,66]. Nearly 75% of the epileptogenic neoplastic lesions are located in or involve the temporal lobe [8,9]. Lesions in the frontal lobe are at least as frequent as lesions in the temporal lobe in patients with neoplasms who do not have seizures [67]. This discrepancy is possibly related to the lower seizure threshold of the temporal lobe, and also to the fact that patients with temporal

lobe partial seizures are more likely to be referred for surgical treatment of epilepsy [9–11]. In a recent series from the Cleveland Clinic consisting of 133 patients who underwent operations for extratemporal epilepsy, tumours were identified in 27.8% of cases; these included, in order of decreasing frequency, astrocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumours (DNETs), glioneuronal hamartomas, oligodendrogliomas and oligoastrocytoma [68].

Brain tumour as a cause of chronic epilepsy

Computed tomography studies in patients with epilepsy have demonstrated a neoplasm in 10–25% of patients with onset of seizures after the age of 40 years and in fewer than 5% of children [69]. During presurgical evaluation of 190 patients with intractable partial epilepsy, Spencer *et al.* [8] detected 15% with a mass lesion, 10% of which were neoplasms. Low-grade gliomas are the most frequent pathological lesions, accounting for nearly 50–70% of all lesions and 70–90% of neoplasms [18,47,66]. Because of differences in the selection and histopathological criteria used in the ascertainment of these lesions, the distributions of the neoplasms according to type have varied widely between series. Nevertheless, indolent or slow-growing glial or neuronal tumours constitute the majority. Although tumours occur more frequently in patients with an onset of epilepsy during adulthood, brain tumours also remain an important cause of intractable epilepsy in children and adolescents as well [32,33]. In a series of 33 children who underwent temporal lobectomy at an average age of 8 years, 48% were diagnosed as having tumours [34].

Gangliogliomas

Gangliogliomas are mixed tumours that are composed of neoplastic glial and neuronal cell types (Figs 70.1 and 70.2) (Table 70.1) [35]. They constitute 10–50% of the neoplasms associated with medically intractable partial epilepsy [35–39]. Seizures are the primary presenting symptom in 80–90% of patients with gangliogliomas [38,39]. Among 11 patients with gangliogliomas, the age at diagnosis ranged between 4 and 69 years [39]. Seizures often occur years before the tumour is detected [37].

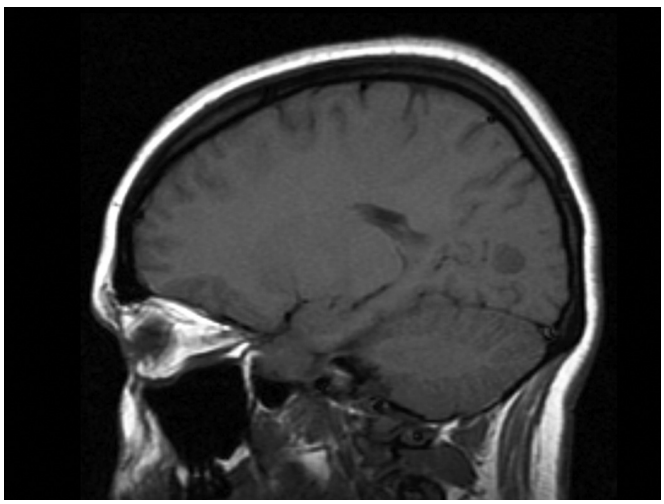
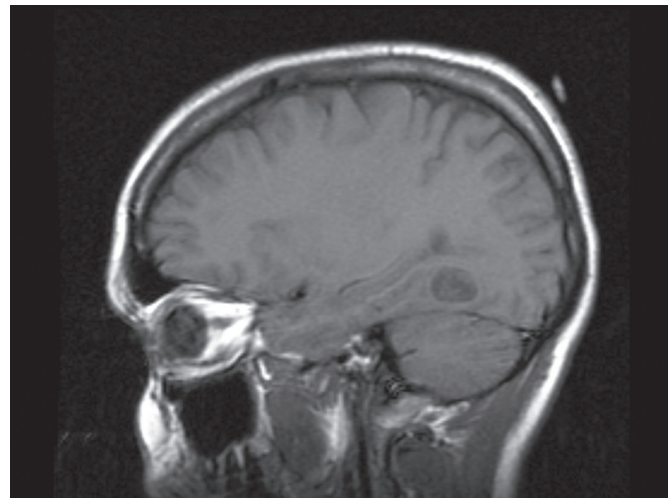
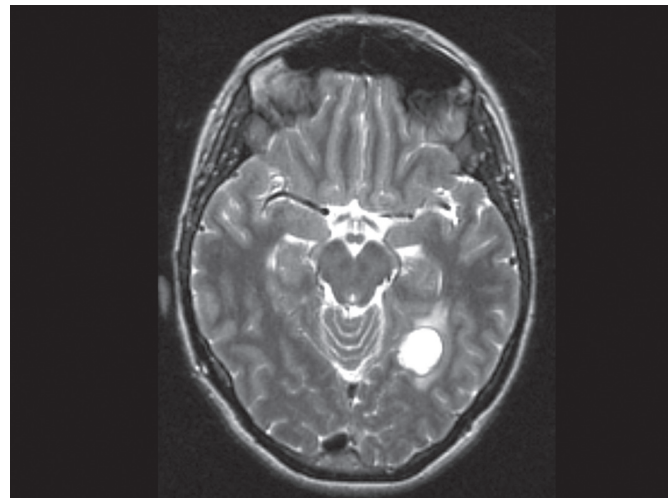


Fig. 70.1 MRI reveals a tumour in the left occipital region in a patient with intractable epilepsy. Pathology revealed a ganglioglioma. There was no recurrence of seizure after resection (sagittal plane T1-weighted image).



(a)



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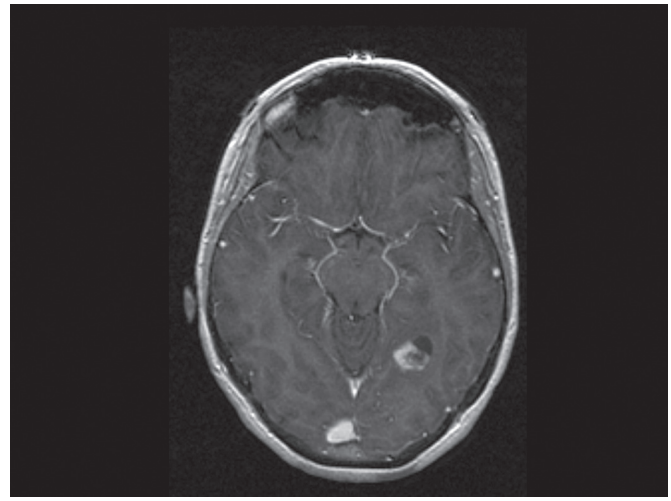


(c)

Fig. 70.2 (a and b) MRI in a patient with intractable epilepsy reveals a lesion in the left posterior temporal–occipital region. A lesionectomy was performed. The pathology revealed a ganglioglioma. Partial enhancement of the lesion is noted (c). The patient was rendered seizure free following resection of the tumour. Note: the left side of the brain is on the right side of the figure. (a) Sagittal plane, T1-weighted image. (b) Axial plane, T2-weighted image. (c) Axial plane, T1-weighted image after gadolinium-diethylenetriamine penta-acetic acid.

These tumours are located within the temporal and frontal lobes in most cases [35–39]. Mesial temporal sclerosis was identified in the hippocampus of the excised temporal lobe in 7 out of 13 children with gangliogliomas and intractable seizures [41]. The surgical approach to resect gangliogliomas, therefore, requires careful preoperative evaluation to delineate the extent of the epileptogenic zone.

Dysembryoplastic neuroepithelial tumours

These morphologically unique and surgically curable neuroepithelial tumours are included in the group of neuronal/glial tumours, grade I, in the new World Health Organization (WHO) classification (Table 70.1) [35]. In one recent series, DNET constituted 8% of the lesions in a sizeable number of patients with neoplasms and chronic medically intractable epilepsy (Figs 70.3 and 70.4) [49]. By contrast, in a recent Maudsley Hospital series, 90% of the neoplasms were interpreted as DNET [36].

In a group of 39 patients with DNET, age at onset of seizures ranged from 1 to 19 years (mean 9 years), and the duration of seizure prior to surgery averaged 9 years (range 2–18 years) [58]. The tumour involved the temporal lobe in two-thirds of patients and the frontal lobe in one-third of patients; parietal and particularly occipital involvement was infrequent [51,58].

Presurgical evaluation

Finding an intracerebral lesion in a patient with recurrent seizures does not necessarily mean that this structural abnormality is producing the seizure activity. The main purpose of the presurgical evaluation in patients with intracranial lesions and intractable seizures is to confirm the relationship between the lesion and the seizure foci. In some patients, the epileptogenic focus is contiguous with but extends beyond the structural lesion [8–11]. The lesion may occasionally be incidental and bear no causal

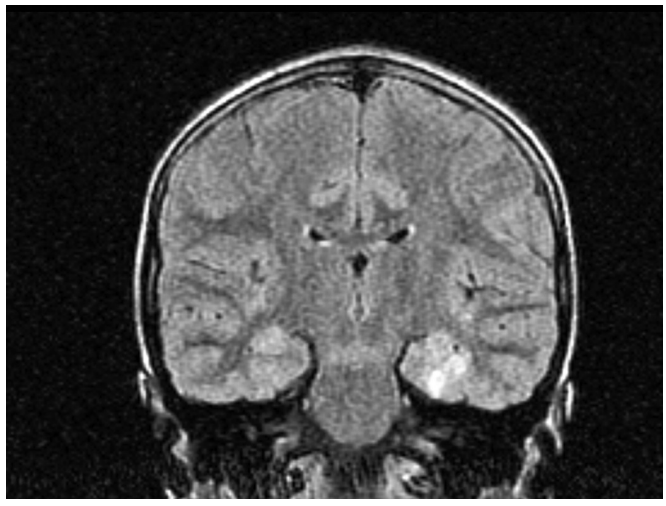
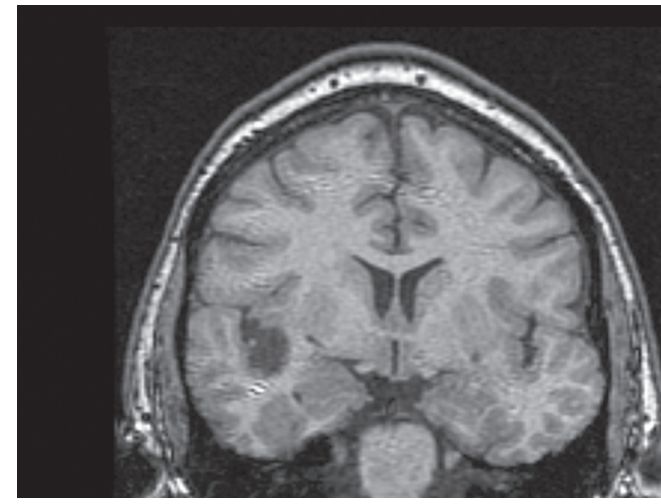
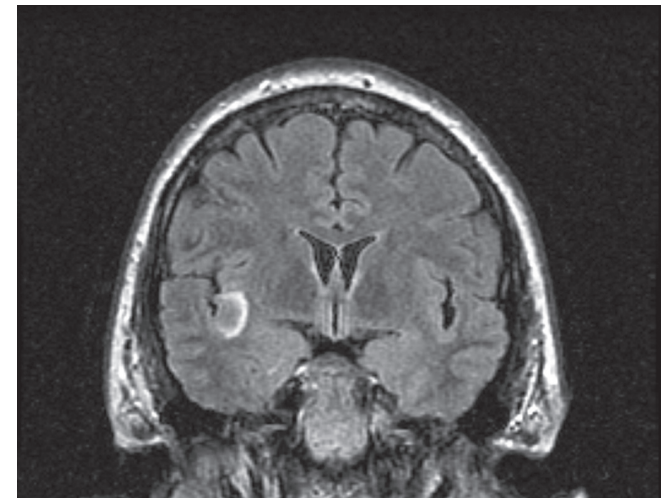


Fig. 70.3 Oblique coronal plane, fluid attenuated inversion recovery sequence. MRI shows a left medial temporal lobe lesion. A lesionectomy and anterior temporal lobectomy was performed. The pathology revealed a dysembryoplastic neuroepithelial tumour. The patient continued to experience recurrent seizures after resection of the tumour. Note: the left side of the brain is on the right side of the figure.



(a)



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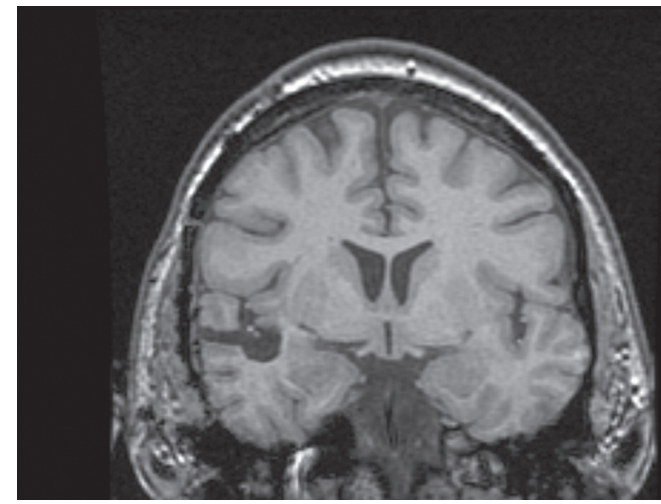


(c)

Fig. 70.4 MRI reveals a right insular lesion in a patient with intractable epilepsy (a,b). The patient underwent complete resection of the lesion (c). The pathology was a dysembryoplastic neuroepithelial tumour. The patient was rendered seizure free. Note: the right side of the brain is on the left side of the figure. (a) Oblique coronal plane, T1-weighted image. (b) Oblique coronal plane, fluid attenuated inversion recovery sequence. (c) Oblique coronal plane, T1-weighted image.

relationship to the epileptogenic focus. Therefore, the understanding of spatial and causal relationship between structural lesions of the brain and intractable epilepsy is essential in planning therapeutic strategies. The preoperative evaluation in patients with substrate-directed partial epilepsy is designed to determine the epileptogenicity of structural abnormalities identified by MRI or other imaging modalities.

Duration of epilepsy

Douglas [70] found that the risk of neoplasm declined precipitously with duration of the epilepsy, whereas Vignaedra *et al*. [71] found no differences in epilepsy duration among patients with and without neoplasms. The majority of patients with lesional epilepsy previously considered for surgery have had seizures for more than 10 years [8–10]; however, today, with the availability of MRI, patients with lesional epilepsies are operated on earlier [11]. No significant difference in the duration of seizures has been observed between patients with neoplastic and non-neoplastic lesions [8–11].

Clinical seizure characteristics

Lesional epilepsy may be associated with simple partial, complex partial or secondary generalized tonic–clonic seizures [8–11]. The most frequent seizure type associated with lesional epilepsy is the CPS [72]. Thirty-four of the 50 patients with intractable seizures associated with space-occupying lesions reported by Boon *et al*. [9] had auras, most frequently epigastric sensations. With the exception of visual auras in patients with occipital lesions, the characteristics of the aura did not help in the localization of the lesion [9].

The most frequent seizure type associated with lesional epilepsy is the complex partial seizure. Williamson [72] has described ictal features of CPS arising from different lobes. Among 50 patients with lesional epilepsy, all of them with a temporal lobe lesion had CPS; however, 74% of patients with extratemporal lesions also had CPS [9]. Seventy-five per cent of patients with temporal lobe lesions had typical temporal lobe seizures [9]. An equally good correlation was shown in patients with frontal and occipital lobe lesions but not in patients with parietal lobe lesions [9]. Seizures originating in the parietal lobe can mimic frontal and temporal lobe seizures [72]. A simple partial seizure as a manifestation of a lesional syndrome, either alone or with CPS or tonic–clonic seizures, was found to be nearly always associated with neoplasms by several workers [8,9]. A change in seizure frequency was not found to be a reliable indicator of a cerebral neoplasm [8]. However, after successful treatment, return of seizures has been an indicator of tumour recurrence that may not be detected radiologically for several months [8,9].

History and examination

A careful history should be taken in all patients, with particular attention to a history of febrile seizures, developmental milestones, head trauma and previous neurological problems. Boon *et al*. [9] noted no significant difference in the frequency of febrile seizures in patients with intra-axial space-occupying lesions and intractable seizures when compared with the general population. Sixteen per cent of the patients with space-occupying lesions and intractable epilepsy had a positive family history of epilepsy, which may indicate an increased susceptibility to seizures in these patients [9]. A thorough neurological examination can detect abnormalities such as a mild hemiparesis or visual field defect that may assist in clinically lateralizing the epileptogenic zone. Facial weakness, especially during emotional expression, may occur in patients contralateral to the epileptic temporal lobe and is uncommon in normal subjects [73,74]. However, clinical examination is non-contributory in most of these patients as a majority of the lesions are small and are detected before any gross mass effect appears.

Age at onset of seizures

Although earlier studies found a low incidence of tumours in patients with onset of seizures before the age of 20 years [75,76], more recent data suggest that refractory partial seizures, even before the age of 20, should raise suspicion of an intracranial mass lesion [8,9]. Blume *et al*. [32] found tumours in 46% of patients under the age of 21 who had undergone surgery for chronic uncontrolled seizures. Among a group of 27 patients with intracranial mass lesions and medically refractory partial epilepsy, age at onset of seizures was the same for neoplastic and non-neoplastic lesions [8]. In a selected series of operated cases, Boon *et al*. [9] found that 78% of their patients who had a neoplasm had seizure onset after the age of 20; however, 70% of patients with seizure onset before the age of 20 also had a neoplasm.

Routine electroencephalogram recording

The occurrence of interictal focal sharp and/or focal slow activity in patients with an intracranial space-occupying lesion has been extensively documented [23]. In patients who presented with intractable epileptic seizures as the main feature of an intracerebral mass, nearly two-thirds had an abnormal electroencephalogram (EEG), and epileptiform activity is more common than slow waves [23]. The absence of prominent focal slow-wave activity in this patient population is mainly a result of the limited circumscribed character of most of these lesions. However, when present, a unilateral focal interictal abnormality was a reliable predictor of, at least, the side of the lesion.

The spatial distribution of the focus coincided with the lesion localization in only 30% of the patients, especially with occipital lesions [77,78]. Epileptiform activity localized by scalp electroencephalography distant from the site of a structural lesion is not uncommon. Salanova *et al*. [77] found that, in a group of patients with frontal lobe epilepsy, scalp electroencephalography provided misleading localizing features in nearly one-third of cases. Patients with temporal lobe lesions were not significantly more likely than extratemporal patients to have an ipsilateral temporal spike or sharp wave focus. Extracranial, interictal and ictal EEG changes were found to be unreliable markers of parietal lobe origin of seizure activity [77,78]. Poor interictal scalp localization has been attributed to the fact that the recorded focal abnormality may be only a part of a deeply localized, more extended focus that propagates to the surface.

The occurrence of bilateral independent sharp waves and spikes in patients with epilepsy has been well recognized [79–81]. In the absence of a detectable lesion, this finding can lead to a decision not to operate on a patient with intractable partial seizures. However, it has been demonstrated that this EEG finding does

not correlate with a poor outcome [81,82]. Nearly 20% of the patients with unilateral structural temporal lobe lesions may show this EEG abnormality, and bilateral independent temporal paroxysmal activity has been observed in patients with extratemporal lesions as well [11].

Long-term video-electroencephalogram monitoring

Long-term video-EEG monitoring may reveal interictal focal paroxysmal epileptiform activity but may be normal or show non-specific changes. Continuous video-EEG monitoring with recording of habitual seizures and careful analysis of the recorded seizures and the simultaneous recorded EEG allows good correlation of clinical events with electrical phenomena. Proper classification of seizure type can be made on the basis of specific, stereotyped signs and symptoms during the attack and the findings on the scalp EEG. In most patients with intracranial lesions detected with neuroimaging, the additional information gathered by scalp EEG-video monitoring is sufficient to consider the lesion as the cause of the epilepsy, and those patients can proceed to surgery without invasive monitoring.

Neuroimaging

Advanced neuroimaging is arguably the most important aspect of the presurgical evaluation of patients with lesional epilepsy because it provides information about the exact location and extent of the lesion. Two structural neuroimaging modalities are used in the identification of potential candidates with intractable partial epilepsy for resective surgery: CT and MRI. The diagnostic yield of the neuroimaging studies depends on the underlying pathology and the anatomical localization of the epileptogenic area. The selection of patients for epilepsy surgery, the presurgical evaluation and the surgical strategy will be greatly influenced by the neuroimaging-identified lesion [8–11].

The importance of imaging patients with intractable epilepsy was obvious shortly after the introduction of CT [83]. However, the limitations of CT in detecting small, benign lesions usually associated with long-standing medically intractable epilepsy soon became apparent [84]. A normal CT scan may not exclude a low-grade glioma, cryptic arteriovenous malformation (AVM), hamartoma or focal cortical dysplasia. In the absence of MRI, CT is a valuable part of the presurgical evaluation of patients with partial seizure disorders. CT may complement MRI in selected patients with bony lesions and calcified intracranial abnormalities. In developing countries, where the availability of MRI is very limited, CT remains the radiological investigation of choice in lesional syndromes.

Investigators at Nottingham University first applied MRI to the study of the brain in 1980 [85]. MRI is the structural neuroimaging modality of choice in patients with intractable partial epilepsy. MRI has been shown to be superior in sensitivity and specificity to CT in identifying the intra-axial structural abnormalities that are associated with partial epilepsy [86,87]. Neoplastic, vascular and infective mass lesions are almost always associated with an MRI-identified abnormality [88–91]. In addition, particular MRI characteristics may help identify the underlying pathology and can demonstrate associated features of calvarial moulding, focal atrophy/encephalomalacia or mass effect. In essence, MRI has been the most successful modality in separating patients with intractable partial epilepsy into two groups: those with substrate-directed and those with non-substrate-directed disease [91]. Patients with substrate-directed or lesional disease have one or more potentially epileptogenic structural abnormalities that may be co-existent with the epileptogenic zone [91].

MRI has been demonstrated to be the most sensitive and specific structural neuroimaging procedure in patients with partial or localization-related epilepsy [11,86–91]. Importantly, MRI is a non-invasive technique that has no known biological toxicity and does not involve ionizing radiation. The presence of an MRI-identified structural abnormality, i.e. MRI-positive partial epilepsy, may suggest the localization of the site of seizure onset [86]. The high diagnostic yield of MRI to delineate foreign tissue lesions, e.g. tumour or vascular malformation, has been confirmed (Table 70.2). MRI findings have been used to select favourable candidates for epilepsy surgery, tailor the operative resection, and confirm the extent of corticectomy postoperatively. The optimal technique in adult patients with partial epilepsy must include coronal or oblique-coronal images using T1- and T2-weighted sequences. Gadolinium-enhanced MRI studies may be useful in patients with primary brain tumours (Fig. 70.2). Selected tumours may be more likely to demonstrate pathological enhancement. Fluid attenuated inversion recovery (FLAIR) sequences have also been shown to increase the sensitivity of MRI to indicate a signal change in patients with foreign tissue pathology.

Table 70.2 MRI and primary intraparenchymal neoplasms.

	PXA	Ganglio	DNET	Oligo	Fibrillary astro	Pilocytic astro
T1 image (intensity)	Hypo, iso	Hypo, iso, sometimes hyper	Hypo	Hypo, iso	Hypo, iso	Solid-hypo, iso; cystic-iso, hyper
T2 image and FLAIR (intensity)	Hyper	Hyper	Hyper (bright rim on FLAIR)	Hyper	Hyper	Solid-hyper; cystic-iso, hyper
Enhancement	+/– (rim and nodule enhance)	+/– (variable)	+/– (faint, punctate in 20%)	+ (patchy and moderate)	+/– (inhomogeneous)	+/– (variable)
Unique features	Cystic, peripheral nodule	Partially cystic enhancing mass	Well-demarcated, wedge-shaped, septations	Calcified with cystic changes and enhancement	Enhance = malignant change	Cystic with enhancing mural nodule

DNET, dysembryoplastic neuroepithelial tumour; fibrillary astro, low-grade fibrillary astrocytoma; FLAIR, fluid attenuated inversion recovery; ganglio, ganglioglioma; oligo, oligodendroglioma; pilocytic astro: pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma.

In an evaluation of 23 patients who underwent both MRI and CT of the head preceding surgery for medically intractable epilepsy, patients with normal MRI all had non-neoplastic lesions [86]. In contrast, in this selected series, all patients with foci of increased signal on T2-weighted MRI images had neoplasms, even when CT was negative. MRI studies are useful for surgical localization and have variable sensitivity and specificity for the major pathological entities, but both are usually greater than 90%, and the diagnostic yield of these lesions has been confirmed in surgical series [86–93]. MRI studies may also be performed to confirm the extent of corticectomy and lesion resection postoperatively.

As stated above, the most common presenting symptom in patients with low-grade and slow-growing primary brain tumours is epilepsy. MRI will reveal a structural intra-axial abnormality in the majority of these patients [92–95]. Imaging features common to all these tumours include the presence of a cortically based lesion, with sharply defined borders, little or no surrounding oedema and, with the exception of pilocytic astrocytomas or gangliogliomas, little or no contrast enhancement. Some lesions may have characteristic, distinguishing features. For example, gangliogliomas are often associated with a cystic lesion and a mural nodule. Although MRI is highly sensitive in detecting neoplasms, it is not specific to particular histopathology. Primary resection of these MRI-identified lesions is associated with a seizure remission in 80–90% of patients [9,10].

MRI-based volumetric measurement of the hippocampal formation [96,97] may provide additional information about the possible sites of epileptogenesis in patients with mass lesions. In a recent study, MRI-based volumetric measurements of the hippocampal formations were correlated with seizure outcome after temporal lobectomy [98]. Volumetric measurements of the hippocampi should now be routine in lesional epilepsy in order to characterize the possible extent of the epileptogenic zone(s), especially given the possibility of dual pathology.

Several centres have incorporated MRI-compatible implantation frames to provide accurate anatomical information for use with intracranial depth electrodes [99,100]. Quantitative MRI-based techniques to assess the extent of cortical resection, and thereby to correlate the extent of resection and patient outcome, have been developed [101,102].

Neuropsychological assessment

A battery of standard neuropsychological tests, aimed at lateralizing and localizing the area(s) of functional abnormality, is administered during preoperative evaluation of patients with intractable seizures [103,104]. In a recent study of patients with intra-axial space-occupying lesions with intractable partial seizures, lateralized neuropsychological findings were congruent with the lesion in 56% but incongruent in 14%; furthermore, localization corresponded with the lobe of the lesion localization in 26% but did not correspond in 30% [9]. Incorrect localizing findings from neuropsychological testing were more frequent when lesions were extratemporal [9].

Intracranial electroencephalogram monitoring

Patients may require invasive monitoring if the results from all previous procedures are conflicting [105,106]. Invasive monitoring is defined as the long-term recording of EEG from subdural and/or intraparenchymal brain areas using intracranial electrodes. This recording technique is generally required in patients with stereotyped partial seizures in whom no consistent epileptiform focus could be demonstrated during the non-invasive monitoring. In patients with known lesions, a subdural or epidural grid consisting of a thin layer of silastic with numerous embedded electrodes is laid over the cerebral cortex in proximity to the neuroimaging-identified lesion [105,106].

However, in addition to morbidity, the apparent lack of sensitivity in localization, especially when subdural grids are placed directly over the epileptogenic lesion, is well documented [11]. Several authors have reported the poor yield of extracranial and intracranial EEG recordings in patients with an epileptic lesion in the parietal lobes [22,79]. Cascino *et al*. [22] studied a group of 11 patients with seizures associated with lesions in the parietal lobe. Out of five patients with a parietal lesion who underwent intracranial monitoring with depth and/or subdural electrodes in an attempt to localize the region of ictogenesis, parietal lobe origin was documented in only two. MRI detected the lesion in all. The authors recommended lesionectomy without chronic intracranial monitoring as an effective and safe surgical procedure in patients with partial epilepsy related to parietal lobe lesions [22].

Functional mapping

The importance of physiological identification of functionally important areas is being increasingly recognized in neurosurgery. Functional imaging of the brain may provide information which may be complementary to that provided by EEG and structural neuroimaging studies. In addition, when neurosurgical procedures are planned in neocortical sensory, motor or speech areas, functional mapping is performed to circumscribe these areas and avoid an unacceptable neurological deficit post surgery. Functional imaging proves most useful when structural pathology cannot be visualized on MRI.

Single photon emission computerized tomography

Computer-aided subtraction ictal and postictal imaging single photon emission computed tomography (SPECT) co-registered to MRI (SISCOM; subtraction ictal single photon emission computerized tomography co-registered to MRI) is a recently developed neuroimaging technique that localizes cerebral blood flow abnormalities and may identify the epileptogenic region, minimizing some of the inherent limitations of direct side-by-side visual comparison of the SPECT and MRI separately [107–111]. The technique utilized at the Mayo Clinic consists of computer-aided subtraction of the co-registered normalized interictal SPECT from the normalized ictal SPECT, followed by the co-registration of the image difference to the MRI. This provides a more sensitive and specific, semiquantitative map of the cerebral blood flow during a seizure.

In a study by O'Brien *et al*. [110] interictal and ictal side-by-side visual interpretation was compared with SISCOM in 51 patients with intractable epilepsy. SISCOM revealed a localized alteration in cerebral perfusion in 88.2% of patients compared with 39.2% of patients using side-by-side visual interpretation. This method has also been shown to be more specific, as determined by con-

cordance with long-term EEG monitoring. The functional change is concordant with the ictal onset zone in approximately 80% of patients [109–111].

Patients with non-lesional extratemporal seizure disorder have recently been found to have a localized SISCOM alteration in 75%. Many patients with extratemporal epilepsy have inconclusive long-term video-EEG monitoring and no lesion on the MRI. SISCOM has its greatest potential in these more difficult cases for localization of the seizure onset.

Detection of peri-ictal hypo- or hyperperfusion localized abnormalities has been shown to reliably locate an epileptogenic focus and select the patients for operative resection. A localized cerebral blood flow abnormality at this potential epileptogenic focus provides a preliminary map and guides the placement of subdural grids/electrodes. Furthermore, the SISCOM images can be transferred across a computer network to the surgical suite where a frameless stereotactic surgical navigation system can be used to localize the SPECT activation in the surgical field intraoperatively. This technique may potentially play an important role in identifying the optimal amount of cortical resection related to epileptogenic lesions.

A recent study from the Mayo Clinic investigated (a) whether the localization of extratemporal epilepsy with the SISCOM technique is predictive of outcome after resective epilepsy surgery; (b) if the SISCOM images provide prognostically important information in addition to those provided by the standard tests; and (c) whether the area of blood flow change on SISCOM images is useful in determining the site and the extent of the excision required for successful postoperative seizure control [107–111]. The concordance of the SISCOM focus with the site of surgery was predictive of an excellent postoperative outcome. Overall, 38.9% had an excellent postoperative outcome and 72.2% had at least a favourable outcome. All patients with excellent outcome except one were seizure free. The exception was a patient who had rare nocturnal seizures. SISCOM localization was concordant with the site of the surgical excision in 52.8%, non-concordant in 13.9% and non-localizing in 33.3%. The concordant SISCOM group had significantly higher rates of excellent and favourable outcome than the other groups. This study also found that one-half of the patients whose ictal scalp EEG was non-localizing had localizing SISCOM abnormalities. These results strongly argue that SISCOM provides localizing information that is in addition to and not redundant for that provided by the more standard tests.

The importance of SISCOM localization in determining surgical outcome has been confirmed in intractable extratemporal epilepsy. Further analysis of these data revealed that the extent of excision of the SISCOM focus is predictive of the success of the surgery. Concordance of the SISCOM focus with the surgical site and the extent of the excision are the only two predictors of the excellent outcome. Many of the patients in this study had SPECT studies because their seizures were not well localized with more standard tests.

Positron emission tomography

Interictal or peri-ictal positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxyglucose (^{18}F-FDG) is included routinely in the presurgical evaluation protocols of many adult and paediatric epilepsy surgery programmes [112,113]. However, PET findings characterized by the increased or decreased uptake of FDG reflect not only the neuronal activity at the site of the ictal onset but also in areas of ictal spread and postictal depression.

Positron emission tomography, when used in the presurgical evaluation of patients with epilepsy, employs either measurements of tissue oxygen consumption (radionuclide ^{18}F-FDG) and/or blood flow [radionuclides $H_2{}^{15}O$ (radioactive water) or ^{15}O]. Tomographic reconstruction locates the sources of gamma ray photons produced after annihilation of the oppositely charged electron and positron that are emitted by the radionuclide. Interictal PET scans may reveal areas of reduced glucose uptake (hypometabolic foci) that correspond to potentially epileptogenic zones.

During a seizure, glucose uptake increases in the area of reduced uptake identified during the interictal scan. The localization of these zones of increased metabolic activity during a seizure is difficult to the point of being impractical. FDG uptake takes place 30–45 min after injection. The seizure must occur early in this period of radionuclide uptake for the focus to be identified. Additionally, FDG has a short half-life. requiring a continuous supply of the isotope during this time. Since seizures are unpredictable, timing limits the utility of ictal PET in localizing seizure foci.

Interictal PET has been shown to be more sensitive than MRI in detecting foci of gliotic tissues with decreased metabolic uptake of FDG. However, gliotic tissue does not necessarily correlate with an epileptogenic region. Only one-third of patients with extratemporal seizures have relevant hypometabolic abnormalities concordant with an abnormal EEG focus [114,115]. These regions of hypometabolic activity are frequently widely distributed and poorly localized [116].

Overall, published clinical series indicate that FDG-PET does not appear to provide additionally clinically useful information in the majority of patients with epilepsy. The continuing development of PET technology may enhance its utility in the evaluation of patients undergoing surgery. The development of receptor-specific ligands (such as ^{11}C-flumazenil) to improve the accuracy of defining seizure foci may lead to future studies relating PET localization to seizure outcome after surgical resection [117–119]. The usefulness of PET in the presurgical evaluation of lesional syndromes will be judged by its sensitivity, specificity and cost compared with other procedures, and how the information provided by PET contrasts with other relatively inexpensive techniques used in presurgical evaluation and in predicting the postsurgical outcome. As PET and other diagnostic technologies are in the process of continuous evolution and improvement, the role of PET in the evaluation of medically intractable lesional epileptic syndromes is unlikely to be settled in the near future.

Magnetic resonance spectroscopic imaging

Whole-brain magnetic resonance spectroscopy imaging (MRSI) is being developed as a functional neuroimaging modality. The usefulness of this imaging technique in the assessment of patients with focal epilepsy is being assessed. In a recent study, phosphorus MRSI correctly lateralized the epileptogenic foci in all eight patients, including a patient with a medial frontal focus [120].

Magnetoencephalography

Magnetoencephalography (MEG) requires complex and costly recording methodology but allows simple interpretation of the field of brain electrical activity [121]. This technique has been shown to map human auditory cortex [122], locations of cortical response to pain and primary and secondary somatosensory cortex [123,124]. With improvement in technology and the availability of simple and less expensive equipment, such localization and quantification of the brain region by non-invasive field measurement may have a major impact in the presurgical evaluation of mass lesions located close to the vital cortical areas.

Invasive cortical mapping

Since the pioneering studies of Penfield and Jasper [7], it has been demonstrated that cortical stimulation of discrete brain areas during neurosurgical procedures is a useful technique for mapping brain areas close to the epileptogenic foci [10,125,126]. Cortical mapping before tumour resection may be required to identify regions involved in critical functions. Because lesions distort the normal topography of the cerebral cortex and vascular landmarks may vary between individuals, cortical mapping may be required to identify regions involved in critical functions. Cortical stimulation techniques have been applied during resection of AVMs and tumours within the language-dominant hemisphere of patients with medically intractable epilepsy [10,125].

Mapping can be done intraoperatively, but this requires that the surgical procedure be carried out under local anaesthetic [125,126]. Alternatively, mapping can be done preoperatively using an implanted subdural electrode array to record both interictal and ictal electroencephalography and to stimulate the cortex at different contact points [10,127]. A major advantage of the grid system is that the patient can fully cooperate in a non-surgical environment and a more elaborate series of functional tasks can be evaluated. Subdural grids of electrodes have also been used for recording cortical somatosensory evoked potentials by stimulating a peripheral nerve to locate the primary somatosensory cortex and to delineate the location of the central fissure.

Electrocorticography

Controversy exists regarding the usefulness of intraoperative electrocorticography (EcoG) to identify and resect the seizure foci versus tumour removal alone. Berger *et al*. [128] analysed 45 patients with low-grade gliomas and intractable epilepsy who underwent EcoG during surgery. Multiple versus single seizure foci were more likely to be associated with a longer preoperative duration of epilepsy. Postoperatively, 41% of the adults and 85% of the children were seizure free without any antiepileptic medication, with a mean postoperative follow-up of over 50 months. Based on their experience, Berger *et al*. [128] advocate EcoG as a useful predictor of seizure outcome in patients with a long-standing seizure disorder. In contrast, among the Maudsley Hospital series of 31 patients who underwent temporal lobectomy for tumour-related epilepsy, postoperative relief of seizures could not be predicted by intraoperative EcoG [36]. The authors routinely perform intraoperative EcoG during resection surgery for epilepsy.

Treatment

Indications for surgery

The widespread and increasing availability of sensitive, non-invasive and neuroimaging techniques means that patients with epilepsy are more likely to be imaged for a structural lesion. The identified lesion may require resective surgery either because of the epileptic seizures refractory to AED or for pathological verification before additional treatment, such as radiotherapy, can be administered.

Patients with medically intractable epilepsy

All patients with medically intractable epilepsy detected by neuroimaging should have 2 years of observation on adequate AED coverage prior to consideration of epilepsy surgery; however, socially disabling seizures, even of 1 year's duration, may necessitate a referral for surgery. Unnecessary AED toxicity and delay in initiating a surgical evaluation may increase a patient's psychosocial debilitation. In contrast, a lesion involving functional cortex may be associated with increased neurosurgical morbidity and surgical management may be deferred.

Patients with well-controlled recent onset or infrequent seizures

Seizure was the first symptom in 164 of 560 patients with a CT diagnosis of supratentorial intra-axial brain tumours [129]. Patients presenting with epilepsy are more likely to have a low-grade tumour associated with a prolonged survival (Fig. 70.5) [8,145]. In these instances, surgery is performed not for the management of epilepsy but to establish a histological diagnosis. It remains controversial whether resection of the tumour either reduces the risk of mortality or improves long-term survival or the control of epilepsy [129]. The controversies in the management of low-grade intracranial neoplasms [130] and the role of radiotherapy [131,132] are beyond the scope of this chapter.

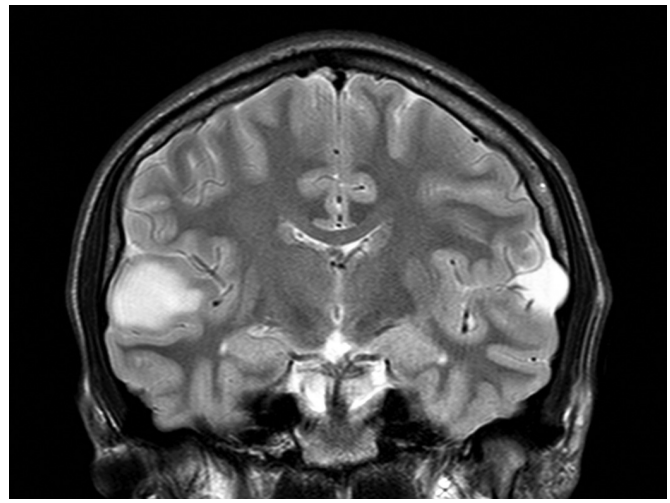
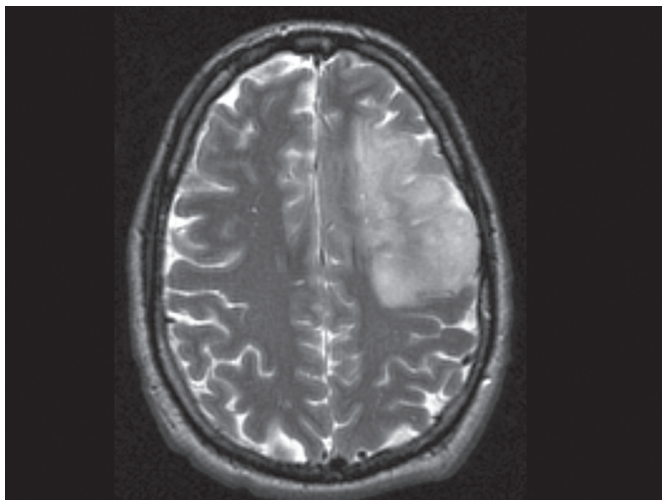


Fig. 70.5 Oblique coronal plane, T2-weighted image. MRI reveals a right temporal lobe lesion in a patient with a chronic seizure disorder that is not disabling. Pathology showed a low grade astrocytoma. Note: the right side of the brain is on the left side of the figure.

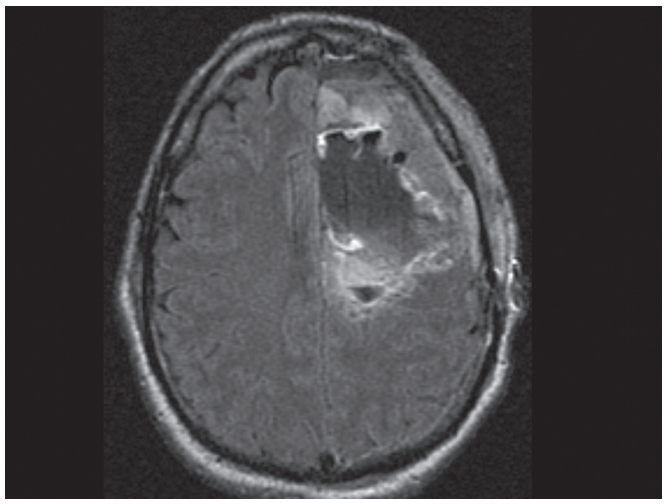
Surgical methods

Resection of the lesion and the surrounding epileptogenic cortex may be carried out by a conventional neurosurgical approach or by stereotactic extirpation of the lesion (Figs 70.4 and 70.6) [92,133,134]. There have been conflicting results regarding the therapeutic efficacy of stereotactic lesionectomy in patients with partial epilepsy [10,92].

A follow-up study of the outcome of stereotactic lesionectomy in 23 patients with mass lesions and intractable partial epilepsy was recently reported [92]. Sixteen lesions involved functional or eloquent cortex as determined by anatomical localization. The mean duration of follow-up was 48.5 months. Out of the 23 patients, 17 (74%) had a significant reduction in seizures and five of them were successfully discontinued from AED therapy.



(a)



(b)

Fig. 70.6 MRI shows a large lesion in the left frontotemporal region (a). A near complete tumour resection was performed (b). The pathology revealed an oligoastrocytoma. The patient had a marked reduction in seizure activity. Note: the left side of the brain is on the right side of the figure. (a) Axial plane, T2-weighted image. (b) Axial plane, fluid attenuated inversion recovery sequence.

Moore *et al*. [135] compared the surgical outcome of anterior temporal lobectomy and stereotactic lesionectomy in 20 and 14 patients, respectively, with intractable seizures operated on at the Mayo Clinic. Seventy-one per cent of lesionectomy patients and 90% of lobectomy patients experienced a worthwhile reduction in seizure tendency.

Outcome

Seizure outcome

The beneficial effect of epilepsy surgery in patients with medically refractory partial seizures associated with structural lesions is well established [7–11]. Postoperative seizure-free rates of up to 83% have been reported, with many of the remaining patients showing a significant improvement in seizure control [11].

The outcome of the surgical treatment of lesional epilepsy is influenced by the nature of the underlying pathology, the completeness of resection of the structural lesion and the extent of the removal of the functionally defined associated epileptic focus [10,11,136]. The relative contributions of these factors and their interactions are difficult to delineate. Moreover, the outcome results from the published series are difficult to compare because of different methods of patient selection, pathological classification, surgical technique and follow-up.

Pathology

LeBlanc and Rasmussen [137] observed in their 108 patients with astrocytomas and other low-grade primary intracranial neoplasms that 70% became seizure free or had a marked reduction in seizures, whereas complete seizure control was unlikely in malignant astrocytomas. Tumour recurrence was often heralded first by a recurrence of seizures after a seizure-free period of variable length [137].

Surgical excision of indolent intra-axial tumours such as gangliogliomas and DNETs is associated with a likelihood of complete or near-complete relief of seizures in nearly 90% of patients (Figs 70.1, 70.2 and 70.4) [36,42]. Out of 15 children, 11 operated on for ganglioglioma and intractable seizures were seizure free over a mean follow-up period of 4 years [138]. These tumours constitute the majority of lesional cases [30]. There is a higher incidence of more benign lesional pathology in intractable temporal rather than extratemporal epilepsy [8].

Completeness of lesion resection

The relationship between outcome and extent of the resection of the lesion is complex and is influenced by the pathology and the extent of the removal of a co-existing epileptic focus. Awad *et al*. [10] studied the effects of the extent of the resection of the structural lesion and the epileptic focus in 47 patients with intractable epilepsy and structural lesions. Complete lesion resection with or without the epileptic focus was associated with a higher chance of a seizure-free outcome than incomplete removal of the lesion [10]. In contrast, despite incomplete tumour removal, 81% of 22 patients from the Maudsley Hospital were completely free of seizures and 10% were almost seizure free during a mean follow-up period of 5.8 years (in this series, DNETs were the most common pathology) [37].

Completeness of epileptic focus resection

Many patients undergoing resective surgery for mass lesions have congruent epileptic foci. Wyllie *et al*. [136] reported better results in those patients in whom the epileptic lesion was fully excised. Extrahippocampal lesions may be associated with cell loss and sclerotic changes in the hippocampus [35,36,39]. Nayel *et al*. [139] reported that the extent of anterior temporal lobe resection may influence the outcome of surgery in patients with posterior temporal and extratemporal lesions.

The factors predictive of a good prognosis in resective surgery for intractable epilepsy guided by subdural electrode arrays and operative EcoG were reported for 64 patients [140]. After 1 year, 70% of the patients with a temporal ictal focus were seizure free compared with 55% of patients with an extratemporal focus. Patients with no postresection spikes had a better prognosis than patients with residual postresection spikes evaluated by operative EcoG. Other factors such as age, gender, duration of epilepsy before surgery, extent of temporal lobe resection and structural abnormalities as determined by MRI were not correlated with a favourable seizure outcome after surgery [140]. However, there are several case reports or small series of patients with congruent epileptogenic foci who became seizure free after surgery limited to the site of structural lesion [10,36].

The goal of epilepsy surgery is to render the individual seizure free without producing surgical morbidity. The primary aim of the treatment should be the removal of the lesion. If complete removal of the lesion cannot be achieved without added risk and morbidity, incomplete lesion removal may provide equally satisfactory results. Many of the tumours associated with medically intractable epilepsy are indolent, with no tendency to progress, and in these cases adjuvant tumour therapy does not appear to be necessary. The relative merits of simple lesionectomy versus additional removal of the epileptic focus in patients with lesional syndromes need further investigation.

Functional outcome

Psychosocial outcomes of epilepsy surgery are a largely neglected field. Little shift in the emphasis of reporting outcome following surgery, other than the seizure frequency, has occurred in recent years. Awad *et al*. [10] reported 47 patients with lesional medically intractable epilepsy showing an association between the extent of the resection of the lesion and seizure control without concomitant indication of whether or how these factors influenced the psychosocial and occupational performance. In a case–control analysis, Gulgvog *et al*. [141] were unable to show any benefit in psychosocial performance in a group of operated patients, despite significant reduction of seizures. In children with intractable epilepsy due to brain tumours treated by surgery, Berger *et al*. [142] reported optimal seizure control in 14 children, but postoperative psychosocial or educational performance was not mentioned.

Psychological outcome

At most epilepsy centres, a comprehensive neurophysiology battery is administered preoperatively and repeated 1 year postoperatively. New material-specific memory deficits are often noted after temporal lobectomy [143]. These abnormalities are usually subtle, asymptomatic and detected only by neuropsychological testing. Dominant temporal lobectomies impair verbal memory, but non-dominant temporal lobectomies impair visuospatial memory [144,145]. This observation indicates that the presence of a contralateral, normal, non-operated temporal lobe is a determinant of the functional outcome. In fact, many patients can show improvement in verbal and visuospatial memory following epilepsy surgery [146,147]. These improvements may be attributed to a significant reduction in postoperative seizure rates and fewer antiepileptic medications.

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71 Resective Surgery of Vascular and Infective Lesions for Epilepsy

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Introduction

Vascular and infective lesions of the brain have a high propensity to induce seizures, and epilepsy is often the main or only symptom. Debilitating and intractable epilepsy presents a strong case for surgical intervention; however, the risk of haemorrhage, overwhelming infection and neurological deficit must be considered. A multidisciplinary approach is encouraged.

The natural history of any disease is of paramount importance in making decisions regarding its treatment. Although vascular malformations have been recognized for hundreds of years, many aspects of their natural history are still unclear due to new diagnostic and treatment options arresting natural progression. The number of infective lesions of the central nervous system (CNS) diagnosed worldwide has increased in recent decades and it is now recognized that infection is one of the major causes of acquired epilepsy [1]. In a recent study of 100 cases of intractable epilepsy in a low-economy country, CNS infection was found to be the leading aetiological factor [2]. Approximately 75% of the world's 50 million epilepsy sufferers live in developing countries and up to 94% of these cases go untreated, largely due to lack of access to appropriate health services [3]. Despite considerable research, little is known about the causes of epilepsy in developing countries [4].

Increasingly sophisticated neuroimaging has improved detection rates of intracranial abnormalities in patients with epilepsy [5] (see Table 71.1 for classification of vascular and infective lesions associated with intractable epilepsy). In particular, MRI is sensitive and specific in distinguishing mass lesions from other pathological entities in patients with epilepsy [6]. If an operable lesion is considered to be responsible for intractable seizures and the relationship between the lesion and seizures is verified, resective surgery can render the patient seizure free and improve his or her quality of life [7]. Although many infective and vascular lesions require emergency surgery in order to save a life, the scope of this chapter is to discuss selective surgery for epilepsy resulting from these conditions. The intent of epilepsy surgery is to improve the quality of life in a population who do not have life-threatening disease, hence a low complication rate is mandatory. As a consequence of the increasingly widespread availability of non-invasive therapies, surgical results are scrutinized with more candour than ever before, and, in the modern era of patient choice, surgery must be without doubt the better option if it is to be offered. In this chapter, current concepts regarding the diagnosis and management of patients with epilepsy associated with infective and vascular mass lesions will be discussed.

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Vascular lesions

Arteriovenous malformations

Arteriovenous malformations (AVMs) are racemose networks of abnormal arteries and veins that communicate directly rather than through a capillary bed, leading to high-flow arteriovenous shunting through one or more fistulae. There is evidence that they are congenital lesions [8,9] although cases of proven *de novo* AVMs have also been described [10].

Although probably first described by William Hunter in 1792, the natural history of AVMs is still not clearly understood. Treatment has traditionally been surgical excision when it is possible to eliminate the risk of future haemorrhage. The natural history in these series is subject to surgical selection and is probably not representative of the natural history of all AVMs. Another confounding factor is a lack of international standards for the diagnosis of AVMs; data from the New York Islands Arteriovenous Malformation Study estimate the incidence at 1.34 per 100 000 person-years, an incidence of first ever AVM-related haemorrhage of 0.51 per 100 000 person-years and a prevalence of haemorrhage in known AVMs of 0.68 per 100 000 [10]. These figures are similar to those of two other major studies [11,12]; in real terms, unruptured AVMs are twice as common as ruptured ones.

It is estimated that between 42% and 50% of AVMs present with haemorrhage [12–14], and that 17–36% [15–17] will present with seizures, with or without associated neurological deficits. The risk of haemorrhage in AVMs has been linked to the epsilon 2 apolipoprotein E genotype [18]. Neurological deficits may occur, and if these are not caused by haemorrhage they can be caused by mass effect on the adjacent brain or by 'steel', in which blood preferentially flows through the shunts in the AVM leading to relatively reduced blood flow in the involved artery's normal distribution [19].

It is generally thought that small AVMs (<3 cm diameter) present more often with haemorrhage than large ones [20,21], possibly because smaller AVMs tend to have higher pressures in the feeding arteries [21]. Several studies between 1970 and 1980 highlight the

Table 71.1 Classification of vascular and infective lesions associated with intractable epilepsy.

Vascular lesions
Arteriovenous malformation
Cavernous angioma
Cerebral aneurysm
Inflammatory/infectious lesions
Pyogenic abscess
Tuberculoma
Neurocysticercosis
Hydatid disease
Rasmussen's encephalitis

benefit of surgical resection for accessible cerebral AVMs in terms of rebleeding and overall morbidity and mortality [22–26]; however, they are, for the most part, in the pre-CT era. This view has more recently been challenged [27] and it has been suggested that a natural history of unruptured AVMs is associated with a significantly lower morbidity than a presentation of haemorrhage. The average bleeding risk is 1.2% per year for unruptured AVMs and 5.6% per year for those with a history of bleeding (at least in the first year following haemorrhage). Subgroup analysis revealed a 0.9% per year bleeding rate for lobar AVMs with superficial drainage [28]. Recent studies suggest that the treatment risk of unruptured AVMs may be higher than the natural history [29], and the morbidity from haemorrhage in those presenting with seizures is less than one-third of that in those who presented with haemorrhage in the first instance [30]. The subject is currently highly controversial and in their 2006 review entitled 'Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy', Stapf *et al.* [31] conclude that 'polar opposites can be found favouring medical or surgical treatment', with 15% differences either way in operative mortality and annual haemorrhage risk between studies. The ARUBA study (A Randomized Trial for Unruptured Brain AVMs), which was started in 2006, is designed to test whether medical management or interventional therapy will reduce the risk of death or stroke by 40% (or about 7.5% per year over 5 years) and aims to randomize 800 patients using intention-to-treat analysis. The outcome of this study is likely to have a significant impact on elective surgery for AVMs.

Seizures are the second most common symptom after haemorrhage. A recent series of 424 patients found increased seizure frequency associated with male sex, temporal lobe AVM, size greater than 3 cm and age less than 65 years [32]; Crawford *et al.* [20] estimated that patients aged between 10 and 19 years had a 44% risk of epilepsy, compared with 31% for patients aged 20–29 years and 6% for patients aged 30–60 years. A significant proportion of patients with cerebral AVMs will develop epilepsy after diagnosis, and the same authors suggested that surgery was the most important risk factor for subsequent development of epilepsy. In their series of 234 patients, the surgically treated group had a 57% risk of seizures compared with 19% for those managed conservatively at 20 years. The 10-year risk was 47% versus 11% for the same groups. No patient with either initial neurological signs or in whom the AVM was a coincidental finding developed epilepsy when treated conservatively [33]. Foy *et al.* [34] found that epilepsy was present in 50% of patients operated on for AVMs after surgery, as compared with an overall incidence of 17% for all patients undergoing supratentorial craniotomies. In earlier series the incidence of postoperative epilepsy has ranged from 4% [22] to 22% [23].

In contrast to these observations, other authors have reported a beneficial effect of surgery on epilepsy associated with cerebral AVMs. Guidetti and Delitala [22] reported that in their series of 130 patients (86 treated surgically versus 44 conservatively) 53% of the surgically treated patients improved, but only 36% of the conservatively managed group improved. Pool [14] found the incidence of epilepsy to range between 30% and 50% in 187 patients who underwent surgical resection, whereas the same incidence was 64% among patients treated conservatively. Trumpy and Eldevik [35] reported that five patients in their series of surgically treated AVMs had no epilepsy following the operation, but five patients developed seizures after surgery. Finally, Murphy found no statistical difference between the percentage of seizure-free patients in the medically treated group and those in the surgical group in his series of 46 patients followed up for a mean of 13 years [16].

Hoh *et al.* [32] report that short seizure history, associated with intracranial haemorrhage, generalized tonic–clonic type, deep and posterior fossa location of the AVM, complete obliteration and surgical resection (as opposed to radiosurgery or embolization) were all associated with a good seizure outcome (Engel class I). Contrasting different treatment modalities, they found an 81% Engel class I result with surgery versus 43% with radiosurgery and 50% with embolization.

The epileptogenic potential is thought to be caused by the tissue adjacent to the AVM, which is characterized by neuronal loss, gliosis, demyelination and haemosiderin deposits [36,37]. Perinidal capillaries have absent basement membranes and this may allow erythrocyte extravasation and subsequent haemosiderin deposition and gliosis in the surrounding tissues [38], which may explain epileptogenesis in the absence of overt haemorrhage. In all the series examined, no mention has been made of any effort by the surgeon to remove surrounding or intervening areas of abnormal brain tissue along with the malformation. Although the importance of preserving normal tissue at surgery is paramount, this approach also has the theoretical disadvantage of leaving the epileptic focus undisturbed. There are as many series reporting good seizure control as there are reporting poor control, and cortical scarring from surgery is a reasonable explanation for postoperative seizures whatever the pathology, so it is unlikely that this will be resolved.

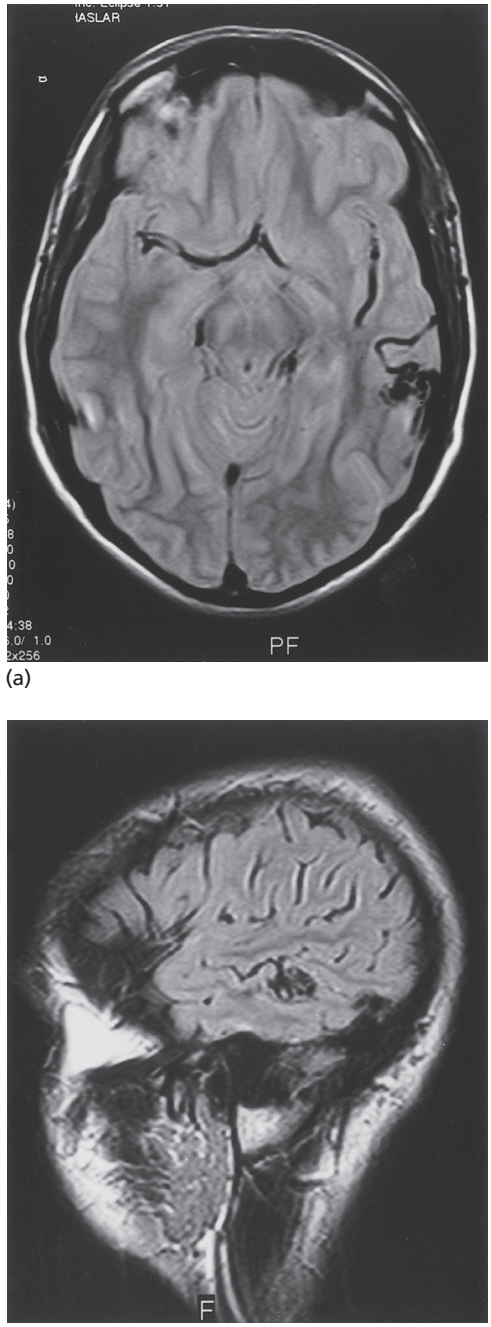
Beside the issue of long-term seizure control, the aim of treatment of AVMs should be to prevent bleeding and reduce long-term morbidity and mortality. It is estimated that the average risk of bleeding from an AVM is around 2–4% per year [39]. For instance, in a study of 166 symptomatic AVMs with 23.7 years' mean follow-up, Ondra *et al.* [30] found that the risk of haemorrhage was constant at 4% irrespective of whether the malformation presented with or without haemorrhage. In the same study, the mortality rate was 1% per year, with a combined major morbidity and mortality of 2.7% per year. In another important contribution, of the patients with cerebral AVMs who survived long enough after the initial haemorrhage to be entered into the Co-operative Study, 53% were reported to have a neurological deficit attributable to the bleeding. Approximately 10% of these patients died as a direct result of their first known haemorrhage

[15]. Twenty-three per cent of the survivors suffered recurrent haemorrhages, with a mortality rate of 12%.

Evaluation

Magnetic resonance imaging followed by cerebral angiography is currently considered to be the gold standard in the evaluation of AVMs. MRI can reveal flow voids on T1- and T2-weighted images, can show the characteristic feeding arteries and draining veins (Fig. 71.1a and b) and can help to differentiate between AVMs and neoplasms, providing the surgeon with vital information in the case of angiographically occult vascular malformations. In nearly all cases, a catheter cerebral angiogram will better outline the characteristics of feeding arteries and draining veins and reveal any associated aneurysms that are present in 7% of AVMs [20] (Fig. 71.2). CT of the brain may show presence of blood around the AVM, as well as possible areas of calcification related to the malformation. It may also reveal pathological contrast enhancement in the area of the AVM itself. With the continuing advances in non-invasive vascular imaging, it is likely that magnetic resonance angiography (MRA) and CT angiography (CTA) will soon supersede catheter angiography.

If surgery is being considered for the treatment of epilepsy associated with an AVM rather than to reduce or abolish the potential for bleeding, every effort should be made to establish the congruence between the area targeted for resection and the epileptic focus. In the majority of patients, scalp EEG alone does not localize or even lateralize the seizure focus. Prolonged EEG monitoring with video correlation of seizures (telemetry), interictal and ictal positron emission tomography (PET), as well as meticulous history-taking and neurological examination, may yield convergent data and therefore augment the accuracy of localization. For obvious reasons, intralesional electrode recordings cannot be made.



(a)

(b)

Fig. 71.1 (a) Coronal view of a MRI scan of a 21-year-old man who presented with generalized seizure activity, showing a left temporal AVM with a large draining vein. There is flow void within the lesion and in the draining vessel. (b) Sagittal view of the same. The scan shows no evidence of previous haemorrhage.

Treatment

Surgery

Epilepsy associated with AVMs can usually be managed with medical therapy, and the presence of seizures in isolation is rarely an indication for surgery. The most attractive feature of surgery for AVMs is that it immediately abolishes the risk of haemorrhage. As has been discussed above, patients presenting solely with epilepsy have a lower risk of haemorrhage than those

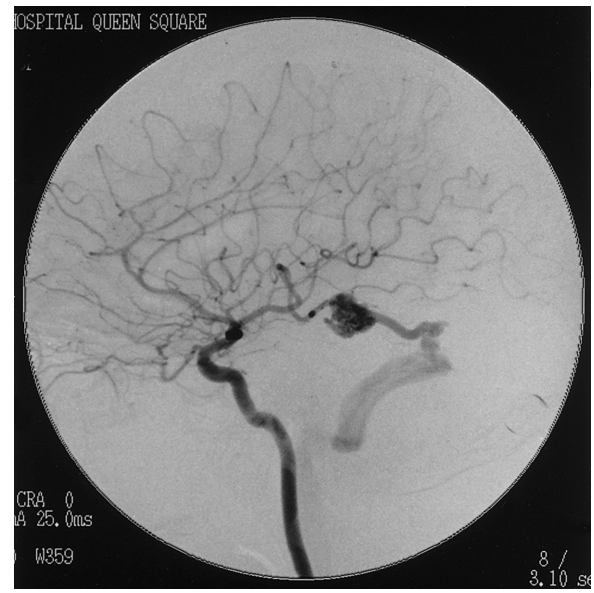


Fig. 71.2 Cerebral angiography of the same AVM (lateral view). The examination shows a single arterial feeder and a single draining vein discharging into the proximal sigmoid sinus. After a failed attempt at embolization the AVM was successfully excised surgically. The patient remains seizure free on phenytoin.

presenting with haemorrhage to the extent that the risk from surgery is greater than the risk of haemorrhage. However, surgery does appear to achieve superior control of seizures compared with other treatment modalities and this may be due to removal of epileptogenic gliosis and blood products during surgery, which does not occur with non-invasive therapies.

The risk of haemorrhage is higher for small AVMs and it has been stated that surgical mortality and morbidity for this group is lower than the projected natural risk [40]. The same authors state that neither seizures nor incipient focal neurological dysfunction alone are indications for surgery, and that the risks of disability or death after the fifth decade of life are probably less than the surgical risks (based on operative mortality of 10% and morbidity of 30%, in 1985). In 1980 a series of 166 consecutive patients found the most favourable operative risk profile as younger than 40 years, absence of neurological deficit, superficial and small AVM in a silent area, female sex and subarachnoid haemorrhage at presentation. The subsequent Spetzler–Martin classification in 1986 reported 100 consecutively operated AVMs and predicted the surgical risk of minor and major neurological deficits based on size, venous drainage and eloquence of involved cortex (small size, superficial drainage and no eloquent cortex predisposes better outcome) [41].

Indications for surgical management of AVMs associated with epilepsy currently include intractable seizures with evidence that the AVM is the cause of the seizures, and seizures associated with an AVM that has previously haemorrhaged. Large or giant (greater than 6 cm) AVMs that are deemed inoperable or an extremely high surgical risk may be transformed into more attractive targets with preoperative embolization.

Radiotherapy

Radiotherapy is an important tool in the treatment of AVMs. Conventional radiotherapy is successful in less than 20% of cases and is therefore not considered effective [42,43]. Stereotactic radiosurgery (SRS) has beneficial effects on both AVM obliteration and seizure control, and photons [X-ray-based linear accelerator (LINAC) systems and gamma knife radiosurgery (GKRS)], heavy charged particles (helium ion Bragg-peak radiation) and proton beam radiotherapy have all been used, although GKRS is the best-established mode of radiotherapy in the treatment of AVMs and is associated with good rates of nidus obliteration and seizure control without the need for fractionation (hence the term 'radiosurgery').

Radiation induces endothelial damage that results in proliferation of smooth muscle cells and the elaboration of extracellular collagen, leading to stenosis of the vessel and ultimately obliteration of the lumen over a period of 1–2 years [44]. SRS is non-invasive in the sense that no craniotomy or brain dissection is required, and it can be administered on an outpatient basis; however, the length of time it takes to work leaves the patient exposed to the risk of rehaemorrhage. Haemorrhages have been documented to occur during the lag period, even in AVMs that had not previously bled, raising the question of whether a partially thrombosed AVM is more likely to bleed because of increased outflow resistance [45]. Several authors suggest that this modality is the best treatment for small malformations located deeply in eloquent areas of the brain [46–48]. It is estimated that between 46% and 61% of AVMs appear obliterated on angiography 1 year after treatment and 86% will be obliterated at 2 years [45]. In a study of 462 patients with cerebral AVM treated with GKRS, 68% of whom presented with haemorrhage and 12.8% with epilepsy, the overall results indicated that seizures improved in 85.5%, were unchanged in 11.6% and deteriorated in 2.9% [49]. In the same study, of the 79 patients (17.1%) who had had a seizure before radiosurgery, 58 presented with seizure as an initial symptom and seizures occurred in the other 21 patients mostly following intracranial haemorrhage. Seizures were either decreased or had disappeared in 91.6% of the former group and in 62.5% of the latter. The authors concluded that radiosurgery is effective not only for the obliteration of the nidus of cerebral AVM, but also for seizure control, even before complete occlusion of the nidus. More recently, a series of 51 patients showed that 51% were seizure free at 3-year follow-up [50]. Another study of 100 patients with AVMs, of whom 33 presented with seizures (11 generalized tonic–clonic, eight simple partial and 14 complex partial), 59% were seizure free and 19% had marked reduction of seizure frequency after radiosurgery [51]. Interestingly, four out of the five patients in this study who had not had obliteration of the AVM on angiography 2 years after SRS also became seizure free, suggesting that structural or biochemical alterations of epileptogenic neurones following radiosurgery may reduce epileptogenicity. Similar results have been reported by other authors [52–54], but new onset of seizures in 1–3% of patients treated with this technique has also been reported [55–57], including one case of acquired mesial temporal sclerosis [58].

The likelihood that radiotherapy will be successful depends on the diameter of the nidus; SRS will obliterate lesions less than 2 cm in diameter 2 years after treatment, although it will obliterate only 50% of lesions with a diameter greater than 2.5 cm. GKRS is less effective for lesions with a volume greater than 10 mL [59]; however, staged GKRS with up to three treatments has been described in patients with larger lesions [60]. Proton beam radiotherapy has been used for lesions greater than 100 mL, with good obliteration rates and seizure control [61]. However, the extreme scarcity of facilities has curtailed its usefulness in clinical practice.

Endovascular treatment

Embolization is also available for the treatment of cerebral AVMs. Although this technique can facilitate surgery, it is generally accepted that it may not achieve permanent obliteration of the malformation because of the high rate of recanalization [62]. It can also induce acute haemodynamic changes in the treated region and multiple procedures may be required to complete the treatment. The complication rate reported by Jafar *et al.* in 1993 [62] for this procedure included a 1.5% risk of severe deficit, a 1–2% risk of death, a 10% risk of haemorrhage and a 3% risk of new-onset seizures. A recent series reported a 90.5% good or excellent outcome but associated with a higher complication risk with a Spetzler–Martin grade III–V [63].

On its own, embolization can achieve a cure in up to 40% of AVMs at best [64], and can also be used as an adjunct to radiosurgery both before [65] and after radiosurgery [66].

Summary

Treatment of epilepsy associated with cerebral AVMs depends on a number of factors, including the size and character of the lesion,

surgical accessibility, locally available expertise and patient choice. Recent studies have demonstrated the comparatively benign course of the many AVMs, and modern antiepileptic pharmaceuticals and advances in radiosurgery have reduced the number of patients in whom surgery is indicated. Close liaison between epileptologists and the neurovascular multidisciplinary team is essential.

Cavernous haemangioma (cavernoma)

Cavernous haemangiomas are well-circumscribed, hamartomatous vascular lesions consisting of irregular-walled sinusoidal vascular channels lined with a single layer of endothelium. They are located within brain parenchyma but do not incorporate intervening neural tissue. There are no large feeding arteries or draining veins. They are thought to grow by a process of vascular cavern proliferation in the setting of repeated haemorrhage [67] and are probably capillary malformations. They have the potential to haemorrhage, calcify or thrombose and are multiple in up to 50% of cases [68]. It is estimated that they constitute 5–13% of vascular malformations of the CNS and they have been found to be present in 0.02–0.13% of autopsy series [69]. The majority present in the third and fourth decades of life; one-quarter to one-third present in the first and second decades [70,71]. Eighty per cent are supratentorial in location [72]. Presentation is most commonly with seizures (79%) and haemorrhage (16%) [72], and the rate of new-onset seizures is 2–4% per year [73].

Autosomal dominant familial clustering can be found in 0.5–0.7% of the population [74] and in 10–30% of cavernous haemangiomas [75]. Sporadic and familial forms are recognized as two distinct conditions, with familial cavernomas associated with a higher rate of haemorrhage and occurring at a younger age [76]. Cavernomas arising in radiation fields following radiotherapy are well documented in children [77]. Other environmental factors, including viral infection, inflammation, immune responses and pregnancy [78], have been reported.

The risk of epilepsy ranges from 4.5% to 11% per year, and this also depends on localization, with greater frequency in the temporal lobes [79]. Relative under-representation in the frontal lobes may be a result of lesions in this area remaining clinically silent; temporal lesions have greater epileptogenicity [72]. Cavernous malformations are twice as likely to be associated with seizures as AVMs or tumours in a similar location, and in a study of 27 vascular lesions associated with intractable epilepsy 74% were cavernous haemangiomas and 14.8% were AVMs [80]. Considering that the prevalence of AVMs is significantly greater than that of cavernous haemangiomas, this finding suggests a greater epileptogenic potential of cavernous malformations. In 1978 Giombini and Morello published a series of 51 cases of cavernous haemangioma and in 19 patients the first symptom was epilepsy whereas haemorrhage was the presenting symptom in 12 [81] (it should be noted that this study was in the pre-CT era). A later (1987) series of 25 cavernous haemangiomas reported that 70% of patients with lesions located within the cerebral hemispheres presented with seizures as the only complaint; 20% had symptoms or signs of raised intracranial pressure and 10% presented with haemorrhage [82].

The haemorrhage rate is estimated at 0.5–3% per year, depending on localization [81], and it is higher in females [83]. In one study of 62 patients with a short follow-up (mean 22.4 months), the haemorrhage risk was estimated to be 1.4% per lesion per annum [84], and in a similar study of 122 patients the bleeding rate was 4.5% for patients with a prior haemorrhage and 0.6% for other presentations [85]. The authors also found that the presence of seizures had no significant association with the risk of haemorrhage.

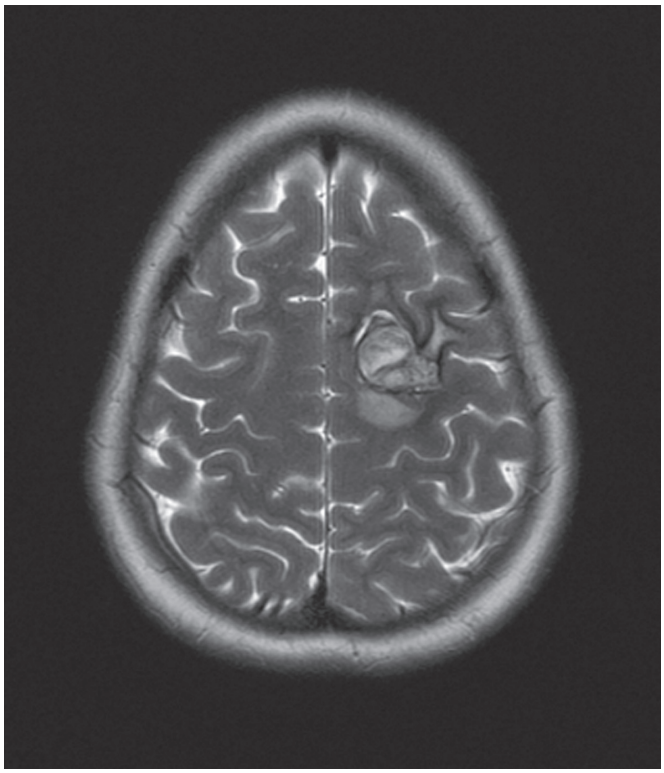
Diagnosis is usually accomplished with CT and more recently and precisely MR scanning. They are the most common angiographically occult vascular malformation and lack large arteries or veins; however, they are commonly associated with developmental venous anomalies (DVAs), which have the characteristic 'caput medusae' appearance on angiography. Typical CT appearances are a well-circumscribed hyperdense lesion. There is usually little or no enhancement [86] but occasionally enhancement is vivid [71]. Forty to sixty per cent are calcified, the surrounding brain appears normal and there is no mass effect unless there is recent haemorrhage; however, CT is negative in 30–50% of cases [86]. MRI is the most sensitive imaging modality and the appearance depends on the age of haemorrhage within the lesion. The most common appearance is a 'popcorn ball' with mixed hyper- and hypointense regions surrounded by a low-intensity haemosiderin ring (Fig. 71.3a). T1- and T2-weighted images have a similar appearance but T2 is more sensitive and may show fluid levels in locules of blood. Contrast-enhanced T1-weighted images demonstrate little or no enhancement [68], unless there is an associated DVA. Gradient echo T2* sequences with a long time to echo (TE) (35 ms) are particularly sensitive to blood products and show 'blooming' of low signal with blood of all ages (Fig. 71.3b). It should be noted that the MRI appearances of cavernous malformations are not 100% specific. The advent of modern neuroimaging has permitted the diagnosis of lesional epilepsy caused by cavernomas which would otherwise have been labelled idiopathic. Lesions presenting solely with epilepsy have probably been under-represented in case series in the pre-CT era.

Pathophysiological mechanisms underlying epileptogenesis include neuronal cell loss, glial proliferation with neuronal death and altered levels of neurotransmitters or secondary messengers [87]. Other mechanisms may include oxygen free radical formation, imbalance of excitatory and inhibitory neurotransmitters, calcium influx and cytotoxicity [88]. The deposition of iron and haemosiderin from blood elicits local gliosis [68,87,89], and iron in particular has been shown to have an epileptogenic effect in animal studies [87,90,91]. A study of low-grade gliomas showed reduced numbers of somatostatin and GABAergic neurones in epileptogenic cortex compared with normal brain [92] but a more recent study using intracellular recording demonstrated different mechanisms of epileptogenesis between cavernomas and neoplasms, with a greater propensity to large spontaneous synaptic events and greater excitation following synaptic stimulation in cavernomas. It is postulated that haemosiderin deposition adjacent to cavernomas can result in impaired glutamate uptake and injury-related synaptic reorganization, allowing focal neuronal hypersynchronization [93]. This may explain the increased incidence of epilepsy in cavernomas compared with other vascular malformations.

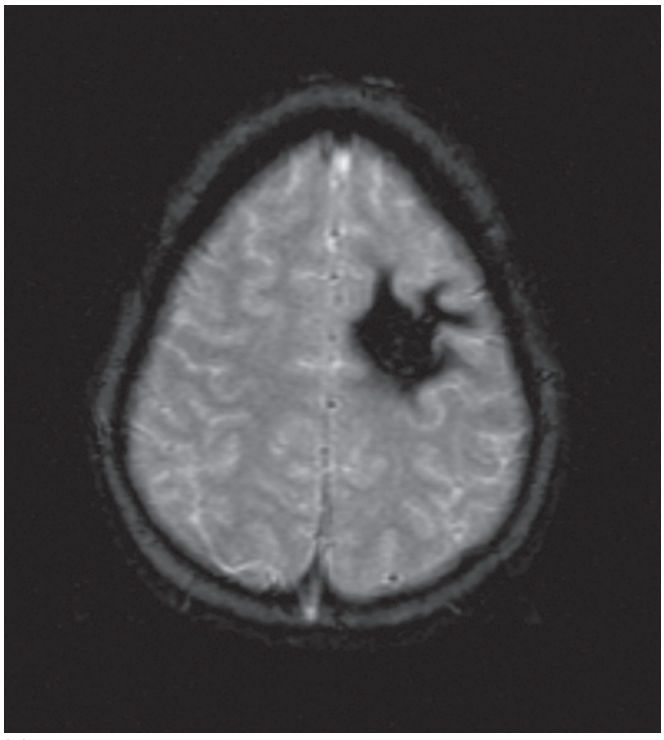
Treatment

Surgery

Although the annual risk of haemorrhage from cavernous haemangiomas is lower than that of AVMs, the cumulative



(a)



(b)

Fig. 71.3 (a) T2-weighted axial MRI showing a cavernoma adjacent to the precentral gyrus in a 28-year-old woman with generalized seizures. (b) The same cavernoma on a T2-weighted gradient echo axial MRI demonstrating low-signal 'blooming' indicating blood products.

lifetime risk for younger patients is still a significant cause of morbidity. It is generally acknowledged that such a risk is higher for patients with documented previous haemorrhage. Several published series show that excisional surgery can be accomplished with low morbidity, with good or excellent results achieved in 82.2–100% of cases [81,82,88]. The results in terms of epilepsy control in surgical series are generally favourable. The meta-analysis of surgical results by Moran *et al* [72] for 268 supratentorial cavernous haemangiomas showed that 84% of patients were seizure free and 8% were improved, with no change in only 6% and with 2% becoming worse. Of the 82% who were seizure free following surgery, 50% were were not taking antiepileptic drugs. In the author's own series of 17 patients, improvement occurred in 13 cases, but four patients remained unchanged with no worsening of seizures. Although seizure control rates in this series are less than in the literature review, this was thought to be a result of the high proportion of patients with intractable epilepsy having been recruited through a formal epilepsy surgery programme, and this illustrates the well-documented finding that intractable seizures are a negative prognosticator for successful seizure surgery [68]. It was also noted that duration of epilepsy negatively affected the outcome of surgery, suggesting that resection should be performed sooner rather than later. A similar suggestion has been made for AVMs [94] and if this is a result of kindling (as has been suggested) then the implication is that seizure surgery should be performed sooner rather than later.

The above review reported that lesionectomy alone yielded seizure control in 92% of cases [72]. Lesionectomy and corticectomy (in which surrounding epileptogenic cortex is also resected) can improve seizure outcome, especially in low-grade gliomas and vascular malformations; however, this may be limited by involvement of eloquent brain. Lesionectomy alone is more likely to be successful in patients with a short and infrequent seizure history that responds to antiepileptic medication, whereas a combined procedure (lesionectomy and corticectomy) may be required for truly intractable epilepsy [67]. Potential functional deficit must be considered when deciding which surgical procedure to offer and individual vocational requirements may guide this. Follow-up in the first year appears to be a good prognosticator of long-term seizure control following surgery [95].

As an alternative to resective surgery, disconnection procedures can offer seizure control in which the epileptogenic focus lies within or involves eloquent areas. Such indirect surgery is not commonly described in the treatment of vascular malformations and, excepting a single case report in which multiple subpial transactions were used in conjunction with excision of a cavernous malformations [96], current literature is devoid of reports.

Vagus nerve stimulation and deep brain stimulation are both neuroaugmentative palliative techniques that are well established in the treatment of intractable epilepsy. However, their role in the treatment of epilepsy arising from vascular lesions has not been described in the current literature.

Radiosurgery

The treatment of cavernous malformations by radiotherapy has been largely focused on brainstem and basal ganglia lesions, and

this is because the morbidity associated with surgical approaches to intrinsic brainstem lesions makes them an attractive target for non-invasive therapies. Histological studies have shown vascular and connective tissue stromal changes, similar to those found in AVMs treated with GKRS, and they have been described in cavernous malformations following GKRS [97]. LINAC-based radiotherapy has produced results similar to surgery in treating epilepsy caused by cavernous malformations [98], but GKRS is used more commonly. GKRS has been shown to be useful in the treatment (decrease in size) of surgically inaccessible lesions in the brainstem and basal ganglia, and has been shown to reduce the annual haemorrhage rate from 33.9% to 12.9% per year in high-risk patients following GKRS [99]. It has also been shown to reduce seizure frequency [100]. Some authors have found rebleed rates to be as high as 33%, with a particularly significant incidence of radiation-related complications [101–103]. However, more recent series show that GKRS can reduce the haemorrhage risk with a 70% cure rate [104]. A multicentre study on the use of a gamma knife for cavernous malformations suggested that, despite the failure of this treatment to protect against risk of rehaemorrhage, there was a beneficial effect on epilepsy, with 53% becoming seizure free, 4% with occasional auras and 20% with a significant decrease in the number of seizures; the remaining 26% were unchanged [105]. The authors found that sex, age and duration of epilepsy had no prognostic value, but that the outcome was better for patients with simple partial seizures than for those with complex partial seizures. Location in the mesiotemporal region was associated with a poor outcome, whereas location in the laterotemporal and central regions was associated with significantly better results. Recent series have reported similar epilepsy cure rates (53% Engel class I or II), combined with effective reduction in the rebleed rate and few complications [106]. Two reviews from 2007 suggest that a benefit of radiosurgery over conventional surgery is unproven for epilepsy. They noted the lack of prospective randomized controlled studies and found higher complication rates in cavernomas treated with GKRS than with radiotherapy for other lesions in similar locations [106,107]. It was also noted that, although GKRS can reduce the haemorrhage risk from cavernous malformations, its superiority over conservative management is not proven.

Modern dose planning targeting the lesion only (and not the adjacent brain) with lower doses has reduced the complication rate; whether this has altered clinical outcome is not yet known. Excellent results have been reported for the treatment of mesial temporal lobe epilepsy associated with hippocampal sclerosis by a gamma knife [108,109]. Although further evaluation of effects of radiosurgery on seizures associated with CMs is necessary, ideally with a prospective study, this form of treatment may be useful for intractable epilepsy related to lesions situated in eloquent and/or inaccessible areas of the brain.

Intracranial aneurysms

Epilepsy is an extremely uncommon presentation of intracranial aneurysm. Although seizures are a well-recognized presentation of subarachnoid haemorrhage, we refer specifically to unruptured intracranial aneurysms causing epilepsy through mass effect on adjacent brain. This is not a well recognized phenomenon; however, it is described in case reports with cessation of seizures coinciding with aneurysm ablation. Aneurysms presenting in this way are likely to involve the middle cerebral artery and/or exert mass effect on the medial temporal structures, giving rise to complex partial seizures [110,111].

Venous malformations

Venous malformations, also known as developmental venous anomalies (DVAs), are best thought of as congenital variations of normal venous drainage. They represent the most commonly documented intracranial vascular malformation by either brain imaging or autopsy, with a prevalence as high as 3% [112]. They can be associated with CMs or, more rarely, with AVMs. On MRI they appear as a stellate vascular or contrast-enhancing mass [113]. Angiography typically shows a caput medusae appearance in the late venous phase [114].

The haemorrhage risk associated with venous malformations is exceedingly low. In a prospective study of 80 patients the bleeding rate per year was calculated to be 0.61%, although the risk of symptomatic haemorrhage was considerably lower (0.34%) [115]. In an older retrospective MRI study, the risk of haemorrhage was estimated to be 0.22% [116].

The risk of epilepsy associated with venous malformation is uncertain. In a retrospective review of MR scanning performed on 1020 epileptic patients, only four had venous malformations [117]. It is also interesting to note that in only two of these cases was there concordance between the vascular lesion and the electroencephalogram (EEG) focus. In another study, by Topper *et al.* [118], of 67 patients with venous angiomas, the concordance was even lower. In their analysis, in only one patient out of 15 who presented with seizures was the EEG found to be congruent with the topography of the lesion. In fact, none of the 67 patients showed an association between the complaints that led to the MR scan and the location of the venous malformation, supporting the view that these are a congenital abnormality of venous drainage of no clinical significance.

Resection of these lesions is generally associated with high morbidity and mortality [119–121], probably because the venous anomaly is a functioning venous channel that drains normal parenchyma, and surgical removal of such channels can thus lead to venous infarction [115]. Similarly, radiosurgery is thought to carry a 30% risk of radiation complications or venous infarctions and may not achieve total obliteration [122].

Capillary telangiectasias

Capillary telangiectasias are often detected as incidental findings at autopsy. They appear as poorly demarcated pink or reddish discoloured lesions with dilated capillaries and may look like a petechial haemorrhage. The intervening parenchyma between the vessels is usually normal and gliosis and microhaemorrhages are absent, distinguishing these anomalies from other vascular malformations [123]. These lesions are extremely rare. In a series of 30 000 autopsies capillary telangiectasias were identified in 0.06% of cases [124]; they represent less than 4% of all angiographically occult vascular lesions [120]. These malformations are usually seen in hereditary haemorrhagic telangiectasias (including Osler–Weber–Rendu syndrome), or associated with other vascular anomalies such as cavernous angiomas. Non-hereditary cases are rare and usually remain asymptomatic [125]. The usual

presentation of symptomatic lesions is haemorrhage or epilepsy, and in a study of 21 patients, seizures occurred in nine cases and haemorrhage in eight [126]. Increasing numbers of capillary telangiectasias are now being diagnosed with more widespread use of MR scanning. Typical appearances include a variable T1 appearance, high signal intensity on T2-weighted images, contrast enhancement and a lack of mass effect. Haemorrhage and calcifications are rare, suggesting that the findings on T2-weighted images are probably related to the presence of deoxyhaemoglobin in slow-flowing blood. They enhance faintly in a 'brush-like' or 'stipple' pattern [127]. The presence of an enlarged vessel in about two-thirds of capillary telangiectasias is thought to represent a draining vein and has led some authors to consider these lesions to be 'transitional malformations' [128]. The brainstem is the most common location [127].

Although seizures may be present in a high percentage of these [120], the number of reported cases is so small that it is likely that these are incidental findings during epilepsy investigation. The absence of cases reported in the literature does not allow us to draw any firm conclusions as to the epileptogenic or bleeding potential of capillary malformations and, on the strength of currently available medical evidence, the discovery of one or more of these lesions during investigations for epilepsy or haemorrhage should not alter the routine surgical or medical management of the underlying pathology.

Infective lesions

In this section, current concepts regarding the diagnosis and surgical management of patients with epilepsy associated with infective mass lesions will be discussed. Emphasis will be on pyogenic brain abscesses, neurocysticercosis (NCC), cerebral hydatid disease and cerebral tuberculoma. Discussion of schistosomiasis, toxocariasis, toxoplasmosis, paragonomiasis and gnathostomiasis is beyond the scope of this chapter.

Pyogenic cerebral abscess

A brain abscess is a focal suppurative lesion within the brain parenchyma. Between 30% and 50% of patients will have a seizure prior to surgical intervention; however, the primary aim of surgery for abscess is not the relief of epilepsy but to save the patient's life by draining the abscess for microbiological diagnosis and reduction of mass effect. A brain abscess may come to the attention of the epilepsy surgeon after resolution of the abscess with an area of cortical scar causing epilepsy. Treatment is then similar to other forms of lesional epilepsy.

Brain abscesses range in size from microscopic foci of inflammatory cells to major encapsulated necrotic areas exerting significant mass effect. Brain abscesses can result in major morbidity and mortality through suppuration alone as well as the effects of raised intracranial pressure from the abscess and associated cerebral oedema. Recent advances in the diagnosis and management of brain abscesses have led to improved survival rates: in the 1950s, the mortality rate associated with brain abscess in the USA was estimated to be 38%. By the 1980s this had fallen to 25%, and the current figure is between 5% and 10% [129]. This reduction has been attributed to improvements in diagnostic imaging (especially CT), neuroanaesthesia and critical care, the evolution of neurosurgical techniques, a better understanding of the pathophysiology and management of raised intracranial pressure and the development of new and more effective antibiotics [130]. Despite these advances, however, brain abscess remains a serious and potentially fatal condition.

The estimated annual incidence of brain abscess in the USA is 1 in 10 000 hospital admissions. Its frequency is one-sixth that of bacterial meningitis and it accounts for 0.7% of all neurosurgical operations. Large postmortem series report brain abscess occurrence rates of 0.18–1.3%. Although historical studies have suggested a male predominance, it is currently thought that there is no difference between the sexes [131]. The median age of presentation is between 30 and 45 years, and this is related to the aetiology; brain abscess due to otitis media has a bimodal age distribution with peaks in childhood and above 40 years. Abscess secondary to paranasal sinusitis commonly occurs between 10 and 30 years of age, 25% occurring in children below the age of 15 years.

Predisposing factors

Brain abscess can develop by direct extension of infection into the brain (this includes trauma and surgery) or by haematogenous spread from remote regions of the body. The most common cause was previously direct extension from the paranasal sinuses or ear. However, with more effective antibiotic treatment of sinus infections, haematogenous spread is now the most common cause. Patients who are severely immunocompromised following organ transplantation or those with HIV are not commonly afflicted by pyogenic abscess, but they are predisposed to cerebral toxoplasmosis, cryptococcal abscess and other atypical organisms.

Direct spread

Chronic middle ear infection is the most common cause of direct intracranial spread (acute infection rarely spreads intracranially). Cholesteatoma is an additional risk factor, increasing the incidence of intracranial extension from 23.2% to 74%. Brain abscesses related to middle ear infection are usually solitary, arising in the inferior temporal lobe adjacent to the petrous temporal bone. Abscess formation may be a result of direct invasion through the dura, bacterial transmission through diploic or emissary veins, or by spread through existing channels, including the internal auditory meatus, cochlear and vestibular aqueducts and temporal suture lines. In contrast to middle ear infections, mastoid infections typically result in abscess formation in the cerebellum.

The majority of abscesses complicating infection in frontal, ethmoidal or maxillary sinuses occur in the frontal lobe, and frontal lobe abscesses are almost always the result of a complication of underlying sinus infection. Sphenoid sinusitis is the least common of the paranasal infections but must be treated with great caution as its complications tend to be more frequent and more severe. Cocaine abuse has been suggested as a risk factor for sphenoidal sinusitis and subsequent brain abscess development [132]. Intracranial abscesses resulting from sphenoid sinusitis tend to occur in either the pituitary fossa or the adjacent temporal lobe.

Periodontal infection is implicated in 6–13% of cases of brain abscess [133]. Organisms spread by either direct extension

through the skull foraminae or by haematogenous seeding. Infection of a molar tooth is more likely to metastasize as it can spread between the muscles of mastication along fascial planes to the skull base. Unlike abscesses that complicate ear infections, most odontogenic cranial abscesses occur following acute rather than chronic infections [134].

Brain abscess is a rare complication of bacterial meningitis in adults; however, it is more common in infants, particularly those with Gram-negative meningitis, and cerebral abscesses have been associated with over 70% of cases of *Citrobacter koseri* (formerly *diversus*) in infants. On this basis it is arguable that all those from whom this organism is isolated from blood or cerebrospinal fluid (CSF) should undergo neuroimaging to exclude an intracranial abscess.

Haematogenous spread

The metastatic spread from distant parts of the body frequently leads to development of brain abscesses. The most common site of origin is pyogenic lung infection, including abscess, bronchiectasis, empyema and cystic fibrosis. Acute bacterial endocarditis is another important cause. Other potential primary foci include osteomyelitis, wound and skin infections, cholecystitis, pelvic infection and intra-abdominal sepsis. In the normal brain, the frontal and parietal lobe receive the majority of cerebral blood flow and bacterial emboli are more likely to be delivered to these areas, lodging at the grey–white junction where cerebral vessels decrease in calibre. They are less well encapsulated, multiple in up to 50% of cases (or multiloculated) and are associated with a higher mortality than those that arise from direct spread (although this may be due to the condition giving rise to the parent infection). The formation of these abscesses appears to depend on the combination of bacteraemia and the presence of an appropriate environment. Areas of infarction, ischaemia and contusion provide a fertile territory for bacterial seeding and abscess formation.

Postoperative abscess

Infection of cranial wounds can lead to formation of a brain abscess. Although it was previously thought that bacterial contamination occurred at the time of surgery, a recent study of paediatric shunt infections suggests that the window of infection extends throughout the postoperative course [135]. Factors influencing infection include CSF leak, implantation of prostheses (including CSF shunts or deep brain stimulation electrodes), systemic steroids (most neuro-oncological patients take steroids during the perioperative period) and the use of intraoperative chemotherapy (Gliadel® wafers, which release carmustine into the tumour bed). If the surgeon has opened the paranasal sinuses or mastoid air cells, the operative site may be contaminated by sinus flora and there is also a potential route for introduction of infection during the postoperative period. If the bone flap becomes infected after a craniotomy, then removal of the bone flap is almost invariably required for resolution of the infection.

Trauma

Brain abscess complicates approximately 3% of penetrating head injuries, especially gunshot wounds. Metal fragments do not pose a significant risk of abscess and do not usually require removal; however, bone fragments have consistently been recognized as an important factor in brain abscess development and should be removed. Several studies of penetrating head injury (combat related) reveal a brain abscess incidence of 3–17% [136] with a mortality rate of 54% [137]. Post-traumatic abscess development can occasionally be significantly delayed: one report describes a brain abscess due to *Clostridium bifermentans* as a result of a metal fragment from a Vietnam War mortar that had been in place for 15 years [138]. In another case, a brain abscess was formed 10 years following a traumatic head injury with retained glass fragments [139].

Microbiology

The species of bacteria responsible for brain abscess depends on the pathogenic mechanism involved. Commonly isolated organisms are streptococci, including aerobic, anaerobic and microaerophilic types. These are found in 60–70% of non-traumatic brain abscesses and many, particularly *Streptococcus milleri*, are part of the normal bacterial flora of the oral cavity, appendix and female genital tract. *Strep. pneumoniae* is a rarer cause of brain abscesses, which are often the sequel to occult CSF rhinorrhoea and also to pneumococcal pneumonia in elderly patients. Enteric bacteria and *Bacteroides* are isolated in 20–40% of cases and often in mixed culture. Anaerobic organisms have become increasingly important organisms, and in many instances multiple species are involved. Gram-negative organisms rarely occur alone. Staphylococcal abscesses account for 10–15% of cases and are usually caused by penetrating head injury or bacteraemia secondary to endocarditis. Clostridial infections are most often post-traumatic. Rarely *Actinomyces* or *Nocardia* species are found to be the causative agent in a brain abscess. Actinomycotic abscess can occur secondary to distant infection, particularly in the chest or oropharynx. *Nocardia asteroides* is an unusual cause of multiple and multilobar thick-walled brain abscess. They are almost invariably associated with pulmonary infection and are often seen in patients with defects in cell-mediated immunity.

Diagnosis

The clinical presentation, laboratory findings and neuroimaging all contribute useful diagnostic information. The clinical presentation of patients with brain abscess depends on the size, location and number of lesions, the virulence of the micro-organism, the host response and the amount of cerebral oedema. There are no pathognomonic features. Parenchymal destruction combined with oedema often results in signs of raised intracranial pressure and focal neurological deficit, but the classical clinical triad of headache, fever and focal neurological deficit is present in fewer than 50% of patients. A constant progressive headache which is refractory to treatment is the most common symptom, occurring in 70–97% of patients [140]. It may be localized to the side of the abscess, but it is often generalized, increasing in severity as the abscess expands. If the abscess is adjacent to the brain surface it may provoke meningeal irritation.

Symptoms of acute infection can be lacking unless there is an active systemic focus. Only 50% of adult patients are febrile at the time of diagnosis and the fever is usually low grade [141]. In children fever occurs in up to 80%, but a high-grade temperature of 38.6°C or more is less common and frequently indicates the presence of systemic infection or meningitis [142]. A reduced Glasgow Coma Scale score is seen in up to two-thirds of patients and presentation ranges from mild confusion and drowsiness to

coma [140]. A relatively late event is papilloedema, which is seen in approximately 50% of patients, and third and sixth cranial nerve palsies may likewise reflect raised intracranial pressure. In most large series, over 60% of patients present with focal neurological deficit [140] and, in a recent analysis of the clinical features of 20 patients with streptococcal brain abscess, nine presented with hemiparesis [143]. Although the majority of supratentorial abscesses (especially parietal) tend to result in hemiparesis, those in temporal lobe cause varying degrees of dysphasia, and visual field deficit and cerebellar abscesses lead to ataxia and nystagmus. Seizures occur in 30–80% of patients preoperatively in larger series, but were a clinical manifestation in only one in 20 streptococcal brain abscesses in one series [143]. Occasionally, brain abscess may mimic a cerebrovascular event; Shintani *et al.* [144] reported a patient in whom sudden-onset homonymous hemianopia was later found to be caused by bacterial brain abscess.

Adults with a normal immune response frequently show a rapid onset and progression of symptoms. Conversely, patients with immunodeficiency may have an insidious onset of symptoms, in which case a high index of suspicion is necessary to make an early diagnosis. Children under the age of 18 months (prior to fusion of the cranial sutures) present with a bulging fontanelle, enlarging head circumference and suture separation, seizures, irritability, nausea and vomiting. Untreated, a brain abscess is usually fulminant, resulting in death in 5–15 days. If the initial picture is suggestive of a focal lesion and rapid deterioration occurs with fever, headache and stiff neck, rupture of an abscess into the ventricle or subarachnoid space should be considered. Abscess rupture is a true neurosurgical emergency and, despite diagnostic and treatment advances, the mortality associated with intraventricular rupture exceeds 80% [144].

Laboratory diagnosis

Routine laboratory studies are of limited value in establishing a diagnosis of brain abscess. The peripheral white blood cell (WBC) count is normal or mildly elevated in 60–70% of patients [145] and blood cultures are likely to be negative unless the abscess is associated with septic embolization from infective endocarditis or a mycotic aneurysm. The erythrocyte sedimentation rate (ESR) is raised in approximately 90% of patients but is non-specific. Serum C-reactive protein (CRP) has some use in differentiating brain abscesses from other intracranial mass lesions [146] and CRP levels have been shown to remain elevated with incomplete treatment, returning to normal after successful treatment. Based on these observations, it is suggested that the return of the CRP to normal coupled with improved clinical condition and CT evidence of abscess resolution should be used as guidelines for discontinuation of antibiotics.

Cerebrospinal fluid analysis is non-specific. There is generally a mild pleocytosis with a WBC count of less than 100/cm^3 unless there is concomitant meningitis [145], and in another study one-third of patients with well-established abscesses had no evidence of pleocytosis. CSF protein is mildly elevated (usually below 100 mg/dL) and cultures are often sterile, especially in patients who are already on antibiotics. Given the limited use of CSF analysis and the presence of an intracranial mass, lumbar puncture is not recommended if the diagnosis of abscess is suspected.

Radiological diagnosis

Advances in neuroimaging, particularly CT scanning, have dramatically improved diagnosis and treatment of brain abscesses. More recently, MRI, magnetic resonance spectroscopy (MRS) and diffusion-weighted imaging (DWI) have emerged as useful tools in the evaluation of patients with suspected brain abscess.

Computed tomography

Computed tomography allows early diagnosis, localization and staging of the abscess according to criteria developed by Enzmann *et al.* [147], who classified abscesses as cerebritis or capsule stage according to patterns of contrast enhancement. Furthermore, they showed that CT classification corresponds well with histopathological stage as confirmed at surgery or postmortem. They noted that the early and late cerebritis phase is characterized by a poorly defined area of low density on non-contrast scans, indicating development of the necrotic centre of the abscess. As the early capsule phase is reached, non-contrast scans demonstrate a faint ring of slightly higher density compared with the necrotic lucent centre and the surrounding oedematous brain. This ring correlates histologically with the developing collagen capsule. Use of corticosteroids significantly reduces peripheral enhancement during the cerebritis stage but has little effect on a mature encapsulated lesion [147]. The characteristic features of the capsule help distinguish ring enhancement due to abscess from that caused by neoplasm. Other features indicative of brain abscess include multiplicity, multiloculation and location at the grey–white junction. Ependymal or leptomeningeal enhancement also favours a diagnosis of brain abscess. With no history of penetrating head injury or craniotomy, the finding of gas within an intracranial lesion is highly suspicious of an abscess involving a gas-forming organism.

These CT findings are not pathognomonic of brain abscess. The differential diagnosis of a ring-enhancing lesion includes tumour, infarction, radiation necrosis and resolving haematoma. With an increasing population of immunocompromised patients, there has been a corresponding increase in the number of abscesses caused by opportunistic infections. Parasites, fungi and atypical bacteria cause a variety of diseases, such as brain abscess (Fig. 71.4), meningitis, meningoencephalitis and granuloma. Because of compromised host defence mechanisms, parenchymal infections may be poorly localized and may fail to become encapsulated [148].

Magnetic resonance imaging

Magnetic resonance imaging is a more powerful tool than CT for the identification of brain abscesses. It has greater sensitivity than CT and is capable of detecting brain abscesses in the earliest stages of development [149]. Some investigators have suggested that, even without the benefit of contrast enhancement, the MRI characteristics of brain abscess are specific enough to make an accurate diagnosis [150]. In addition, MRI can better demonstrate anatomical detail and multiple imaging planes. The MRI features of brain abscess, like CT features, are related to the pathological phase of the abscess. On T1-weighted images, a peripheral zone of mild hypointensity relative to adjacent brain is seen, representing oedema formation. This surrounds a core of more marked signal hypointensity, which equates to the necrotic centre of the abscess. Between the two regions is the capsule,

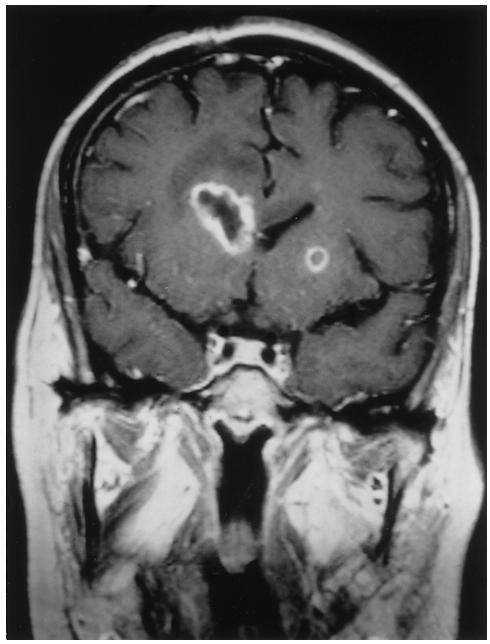


Fig. 71.4 *Aspergillus* abscesses in a 38-year-old immunocompromised man.

which appears as a discrete rim that is isointense to mildly hyperintense, and enhances vividly with gadolinium. This enhancement is frequently the most reliable diagnostic criterion in the acute setting (Fig. 71.5). On T2-weighted images, the signal intensity of the oedematous region increases markedly compared with the adjacent brain, and the centre is isointense to hyperintense compared with grey matter. The capsule has better definition and is seen as a hypointense rim at the margin of the abscess. Finally, one author has suggested that MRI is more specific than CT in differentiating oedema from liquefactive necrosis, which is valuable for planning the timing of aspiration [151].

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy has emerged as a useful technique for the differentiation of a brain abscess from neoplasm [152]. It is non-invasive and can be added to routine MRI examinations with only a minimal increase in cost and time [153]. *In vivo* MRS, when combined with MRI, can help to characterize cystic intracranial mass lesions [154]. Lesion-specific spectral patterns may assist in tissue characterization, for example they permit differentiation of brain abscess from necrotic or cystic tumours [155]. Compounds seen in MRS spectra of abscesses are often absent from tumour spectra. Intracranial tumours demonstrate resonance lines from lactate, choline and lipid, whereas abscesses demonstrate resonance lines from succinate, acetate and several amino acids derived from extracellular proteolysis or bacterial metabolism.

Diffusion-weighted imaging

Diffusion-weighted imaging can differentiate between abscess and tumour or infarct when the diagnosis is uncertain, despite CT or MRI. Ebisu *et al.* [156] examined the diagnostic ability of DWI to differentiate brain abscess from necrotic or cystic tumours. In previous studies, necrotic or cystic tumours showed low signal intensity on DWI, indicating a high apparent diffusion coefficient (ADC). Ebisu *et al.*, in contrast, observed high signal intensity in abscess fluid, associated with low ADC.

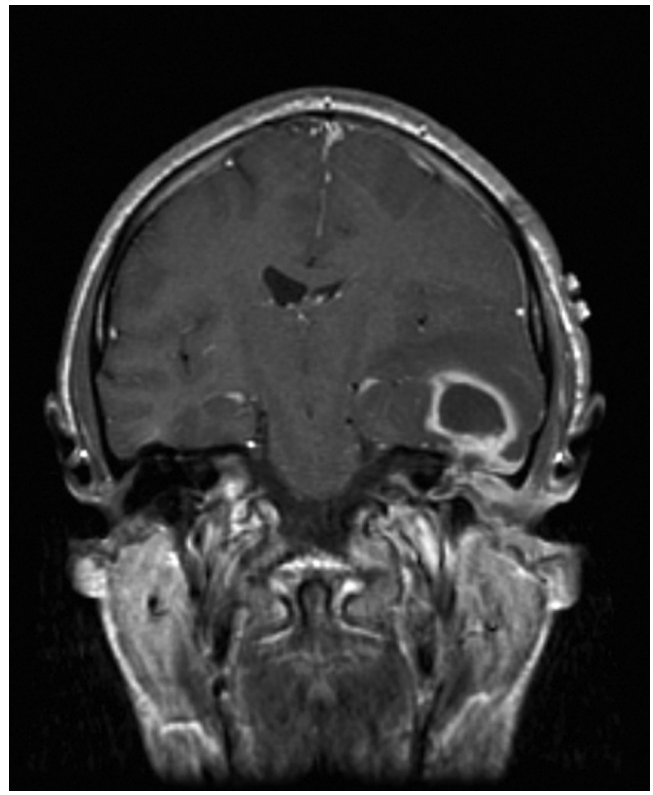


Fig. 71.5 Gadolinium-enhanced T1-weighted coronal MRI showing ring-enhancement of an abscess in the inferior temporal lobe on the left. There is associated enhancement of the middle ear cavity adjacent to the abscess.

Surgical management

Until the early 1970s, surgery (aspiration, drainage, excision) was considered the method of choice in the management of brain abscess. Later evidence, however, suggested that selected patients, especially those in the early cerebritis stages, could be managed successfully with antibiotics alone [156,157]. Heineman and Braude [158] were the first to suggest that a brain abscess could be treated successfully without surgery, reporting six patients with brain abscesses who were cured with antibiotics alone. Rosenblum *et al.* [157] reviewed five large series concerning non-operative management of brain abscess. Overall success rate was 74%, with a mortality rate of 4% among a total of 50 patients.

Although non-surgical management can be effective, the ease and safety with which abscesses can be aspirated through a single burr hole using modern image guidance techniques means that it is usually preferable to obtain cultures and confirm the diagnosis. Rosenblum *et al.* [157] found that no abscesses over 2.5 cm in diameter resolved without surgical intervention, and Black *et al.* [159] found complete failure of antibiotic therapy alone for large abscesses despite adequate concentrations of antibiotics in the abscess cavity. This is of particular relevance to immunocompromised patients, who may harbour opportunistic infections not responsive to conventional antibiotic therapy. Removal of

purulent matter provides the additional benefits of immediate reduction in mass effect and intracranial pressure and a more favourable environment in which antibiotics can work (many antibiotics are rendered ineffective by the acidic environment within an abscess cavity). Non-operative management without an attempt to culture abscess material directly, therefore, has a limited role, especially given that there are few instances in which aspiration of a suspected abscess for culture is not feasible or possible.

The optimal definitive surgical management of brain abscess, in terms of its aims and techniques, remains a subject of controversy. Various procedures have been utilized, the most common being continuous tube drainage, stereotactic or open aspiration, open drainage and washout [160], marsupialization of the abscess and craniotomy with complete excision [161]. At present, drainage either open or via a tube and marsupialization are rarely used. Aspiration and excision are the mainstay of surgical treatment; however, controversy continues regarding optimal treatment. Although many surgeons have particular preferred methods, choice of one procedure over another may be influenced by patient factors, such as age, neurological and general medical condition, stage and type of abscess and whether multiple lesions are present. Aspiration alone has led to excellent outcomes in several reports [162,163] and in combination with appropriate antibiotics is considered by many to be the procedure of choice [145]. In the majority of cases aspiration establishes the diagnosis and provides culture material for antibiotic sensitivities. Large abscesses can be completely decompressed with minimal trauma and immediate reduction in mass effect. CT- or MRI-directed stereotaxis and ultrasound guidance (particularly useful for supratentorial lesions over 15 mm in diameter and in infants through an open fontanelle) [164] have all been described. Stereotactic aspiration is particularly suited to deep-seated or multiple abscesses and abscesses situated in eloquent areas of the brain where open operation would cause neurological damage. Factors shown to be related to failure of this approach include inadequate aspiration, lack of catheter drainage of larger abscesses, chronic immunodeficiency and insufficient antibiotic therapy.

Direct instillation of antibiotics into the abscess cavity during aspiration has frequently been employed, but the benefits of this practice are ill defined. Although there is as yet no direct evidence that this practice hastens abscess resolution, it has been shown to reduce wound infection rates [165], and it is argued to be a useful adjunct in cases of recurrent or refractory abscesses. Instillation during the early cerebritis phase may be deleterious in that the irrigating fluid can promote spread of infection to surrounding tissues [159]. Also, high local concentrations of some antibiotics (especially β-lactams) can cause seizures.

The most common complication of aspiration is intracranial haemorrhage. This occurs in the region of the developing collagen capsule, which contains friable vessels. Haemorrhage is a more common event in patients with cyanotic congenital heart disease.

Although aspiration has clearly proved successful, some surgeons favour excision via formal craniotomy, especially for cerebellar abscesses. Formal excision is inappropriate for lesions in the cerebritis phase, for deep abscesses and for those located in eloquent region when aspiration can be performed with relative ease. Multiple lesions are generally not amenable to excision. If the abscess is associated with a foreign body (especially bone fragments from penetrating trauma) surgery is often required to remove the foreign body, otherwise recurrence of the abscess may occur [166]. Fungal abscesses usually require excision as hyphae tend to aggregate within the capsule, making eradication difficult. Abscesses caused by mould are generally limited to severely immunocompromised patients. They require excision but are associated with a very high mortality.

Some authors recommend that all gas-containing abscesses be excised on the basis that, although gas-forming bacteria are occasionally responsible, the gas is more often a result of a fistula into the paranasal sinuses or middle ear. One study examined five patients in whom gas was found in the abscess cavity, all of which were eventually found to have an extracranial communication that required repair [167].

The role of surgery differs in the case of multiple abscesses. These are most commonly encountered in patients with cyanotic heart disease and other forms of haematogenous spread. In one series the incidence was said to approach 50% [168] with a mortality of 32%, failure to control intracranial and systemic infection being the main source of mortality. Because multiple abscesses tend to be smaller, the role of surgery is primarily diagnostic rather than curative. If there is one large abscess causing significant mass effect then this may be considered for operation, and in some patients with multiple abscesses aspiration of pus can be a life-saving measure [168]. Mamelak *et al.* [131] suggest that the combined approach of appropriate antibiotics, elimination of the primary septic focus and liberal use of CT to anticipate intracranial complications should yield cure rates of over 90% – a result similar to that expected when treating patients with solitary lesions.

As an adjunct to surgery, corticosteroids have been used to attempt to reduce cerebral oedema; however, steroids have been shown to inhibit leucocyte migration and impair host defence mechanisms that help to contain the infection. In experimental animal models of brain abscess, the collagen capsule in dexamethasone-treated animals did not develop [169] or development was delayed [170]. In addition to this, corticosteroids appear to reduce the degree of contrast enhancement on CT scan, especially in the early cerebritis stage [171], hence those treated with corticosteroids cannot reliably be assessed on the basis of reduced contrast enhancement. In most hospitals steroids are currently used only in those patients in whom significant mass effect is thought to be responsible for neurological deficit. Steroid treatment should be continued until the neurological condition stabilizes and then it should be tapered.

Despite the reported success with non-operative management as well as various forms of surgery, there is no consensus as to what constitutes optimal management of brain abscesses. No strict protocols can be devised; each case must be treated individually on its own merits, taking account of the factors described above. However, the general aim in the acute situation is elimination of active suppuration. Consideration of long-term effect on seizures is less of a priority.

Outcome

Thus, despite the best efforts, even successfully treated brain abscesses can result in long-term neurological morbidity [172,173], and this is most frequently related to seizures, cognitive dysfunction and focal neurological deficit, with up to 50% of patients suffering permanent neurological deficit [174]. The single most

important factor influencing mortality is the neurological condition of the patient at the time of diagnosis [145]. Patients who are alert with minimal deficits tend to have a good outcome, whereas mortality rates are much higher in patients who present in obtunded or comatose states.

The reported incidence of epilepsy following brain abscess is between 30% and 80%. One study in which 72% of patients developed late epilepsy also showed that all the patients who had seizures preoperatively went on to develop late epilepsy. The mean onset time of seizures for patients in this group was 3.5 years, although this was age dependent: in the 20- to 40-year age group, seizures began on average 1.7 years after diagnosis, compared with 4.4 years for patients below 20 years of age. In fact, 50% of patients in the older group had their first seizure during the first year after diagnosis compared with only 20% in the younger group. Analysis of seizure frequency showed that the maximum frequency occurred during the fourth and fifth years post diagnosis, and this peak correlated well with the occurrence of epileptogenic EEG patterns [175]. It has been suggested that the risk of developing late seizures is related to the location of the abscess. Nielsen *et al.* [173] found a higher incidence of seizures with frontal lobe abscesses, but other authors report no such relationship [130]. There is some evidence that there is a reduction in seizures among patients treated with aspiration as opposed to excision [146,176].

Summary

The majority of seizure disorders occurring after a brain abscess are relatively well controlled with AEDs. For those that remain intractable to maximal medical therapy, seizure focus resection may be considered [145]. Given the high likelihood of developing seizures, all patients with supratentorial brain abscesses should routinely be placed on prophylactic AEDs to continue for 1–2 years as directed. They may then be tapered, providing that the EEG shows no epileptogenic activity.

Neurocysticercosis

Background

Despite voluminous literature on neurocysticercosis (NCC), it is a disease that is unlikely to be familiar to most clinicians in the UK and Western Europe [177]. Worldwide it is the most common parasitic disease of the central nervous system (CNS) and a major cause of epilepsy and death in endemic areas, including Mexico, India and China [178]. Epilepsy is the most common clinical manifestation and presenting feature of NCC [179]. With the exception of south-west USA, it is very rare in industrialized nations [180], and prevalence is highest in Latin America and South-East Asia. It may be endemic in sub-Saharan Africa, although few studies have been carried out [181]. Reports show that NCC is still a significant cause of epilepsy in Ecuador [182], Honduras [183], Brazil [184], Cuba [185], Colombia [186] and Peru [187] and a resurgence of cases of epileptic seizures associated with NCC has been reported in Indonesia [188]. It is being diagnosed more frequently in developed countries as a result of tourism to countries where the disease is endemic [189]. NCC causes enormous human and economic cost owing to medical resources, AEDs and lost production. It has been proposed that NCC should be an internationally reportable disease [190].

Neurocysticercosis is a helminthiasis caused by the encysted larval stage, *Cysticercus cellulosae*, of the pork tapeworm *Taenia solium*. In the first stage, a human (the definitive host) ingests undercooked pork containing viable cysticerci, from within which the scolex hatches in the gut and attaches to the intestinal mucosa. Over 3 months, the tapeworm matures to a length of 2–7 m and gravid segments are released into the faeces. Following ingestion by a pig (the intermediate host), the eggs hatch in the small intestine, burrow through the wall and enter the CNS and the striated muscle, where they develop. When humans become intermediate hosts by accidental ingestion of eggs (faecal–oral spread), the life cycle is completed in a similar way in the CNS, skin and muscle of the human [177]. Postmortem studies of expatriates from endemic zones have improved our knowledge of natural human infection and it is now known that parenchymal cysts usually lie dormant for many years, and symptoms usually coincide with larval death and an intense inflammatory response caused by the release of larval antigens. A solitary parenchymal lesion is the most common form and seizures are the most common symptom, presenting in 70–90% of patients. Lesions may be multiple and can cause significant mass effect, hydrocephalus, basal arachnoiditis and cerebral infarction. In time, cysts tend to shrink, resulting in granulomata, which either calcify or disappear completely [180]. This pattern of spontaneous resolution has important implications for the correct diagnosis and treatment of the disease.

Diagnosis

A thorough history and neurological examination may yield clues, but there is a wide variation in the clinical manifestation of NCC. Seizures are the most common symptom and may occur when a cyst is degenerating or around a chronic, calcified lesion [179]. Other common presentations include symptoms of raised intracranial pressure. CSF usually shows increased protein and pleocytosis (eosinophils are not always raised). Electroencephalography is unreliable and may show generalized, focal or no abnormalities. A study of interictal EEGs in 50 patients with epilepsy and evidence of NCC showed that the EEG was normal in patients with inactive forms of NCC but was abnormal in 50% of patients with active and mixed forms, and in 48% of patients with active forms only [191]. EEG abnormality was independent of multiple lesions.

Ten to twenty per cent of patients will have intraventricular cysts. These may cause hydrocephalus and can be accompanied by nausea and vomiting, headache, ataxia and confusion. Focal neurological deficits are uncommon. Cysts within the basal cisterns can present with signs of meningeal irritation, hydrocephalus, vasculitis and stroke. Rarer neurological manifestations, such as altered mental state, spinal NCC with radicular pain, paraesthesiae or cord compression, migraine, ophthalmic cysticercosis and neurocognitive deficits have all been reported. Cysticercal encephalitis with multiple parenchymal inflammatory cysts and diffuse cerebral oedema has been described in young girls and such patients are at risk of severe neurological sequelae. In India, solitary enhancing CT lesions are particularly common but meningeal NCC has a much lower frequency [192]. The reasons behind this are unclear.

Cerebral tuberculoma is the main differential diagnosis and criteria for differentiation are described by Rajshekar *et al.* [193].

In a series of histopathologically diagnosed cases, intracranial hypertension and progressive neurological deficit were not seen with NCC. NCC lesions were well circumscribed, less than 20 mm in size and not associated with midline shift. Tuberculomas are, by contrast, usually irregular, solid, greater than 20 mm in size and present with a progressive deficit. This distinction is very significant for management; parenchymal cysticercosis is a benign and mostly self-limiting condition, but a tuberculoma is an active infection that requires prolonged therapy with potentially toxic drugs.

Neuroimaging is crucial to diagnosis, CT being particularly useful for showing calcified inactive lesions. MRI is superior for demonstrating subarachnoid or intraventricular cysts and for showing inflammation around a cyst [194]. Cysts may be single or multiple and at different stages at any given time. A classification system that corresponds to parasite viability has been proposed by Carpio *et al.* [195]: active, transitional and inactive. In the active stage (cyst asymptomatic) the CT appearance is a rounded hypodense area, or there may be a CSF-like signal on MRI. The 'starry night' effect (the presence of multiple eccentric mural nodules) is characteristic of NCC, although it may also be seen in cases of *Toxoplasma* infection. The transitional stage is a result of cystic degeneration. This appears on CT as a diffuse hypodense area with an irregular border that enhances with contrast. They appear as low-signal areas on T2-weighted MRI. Lastly, with the death of the scrolexes within the cyst, it either disappears or becomes a calcified inactive nodule of low intensity visible by proton-weighted MRI or homogeneous high density on CT scans.

Standard enzyme-linked immunosorbent assay (ELISA) techniques have proved less useful than hoped because of high false-negative and false-positive rates. Newer enzyme-linked immunoelectron transfer blot (EITB) assays on CSF or serum appear to have higher sensitivity (98%) and specificity (100%) in Latin American samples [196] but are less accurate for solitary enhancing CT lesions in India [197], Ecuador [198] and Honduras [182]. Its superiority to ELISA is a result of its ability to detect up to seven glycoproteins specific to *Taenia solium*. It is visualized like a Western blot, so that non-specific bands can be ignored, thereby ruling out cross-reactivity. More recently, an antigen detection 'capture' assay specific for viable metacestodes in CSF has been designed [199] and so far this has proved to be the most reliable method of detecting active cases of NCC.

A satisfactory international diagnostic protocol has yet to be agreed upon [200], although this was addressed recently by a panel led by Del Brutto *et al.* [201], who have summarized diagnostic criteria and degrees of diagnostic certainty (Tables 71.2 and 71.3). Criteria are divided into categories based on the weight attached to each feature: absolute, major, minor or epidemiological. Data interpretation allows the calculation of three degrees of diagnostic certainty – definitive, probable and possible. Since spontaneous cyst resolution is typical of NCC, it has been suggested by another group that this is also included as a minor criterion [177]. The most effective approach to NCC infection is prevention and this should be a primary public health focus for all developing countries [195].

If NCC is suspected clinically then antihelminthic drugs should be started without biopsy, and if seizures occur then these should be treated medically. It is not general policy to use albendazole and praziquantel with single enhancing lesions because the cysticerci are, by definition, dying away and will resolve spontaneously [180]. Good seizure control is usually achievable with a single lesion.

The management of NCC depends on the degree of neurological impairment, location, size and viability of the cysticerci, and the extent of the immune response [202]. Treatment of individual cases is based on anatomical location (parenchymal, subarachnoid, intraventricular, ocular or spinal) and mixed forms of NCC constitute more than 50% of cases. Therapy for mixed forms should address the most serious or life-threatening lesion first, including lesions causing raised intracranial pressure, hydrocephalus (of any mechanism), meningitis caused by subarachnoid NCC, cysticercal encephalitis and spinal NCC with myelopathy. These have been labelled 'malignant' because of their high morbidity and mortality rates. Benign forms of NCC include parenchymal cysts or calcifications without associated hydrocephalus, and chronic meningitis. Surgical excision is occasionally indicated for large solitary parenchymal cysts that exert local mass effect or cause raised intracranial pressure [203]. It is also indicated in cases of focal, medically intractable epilepsy that can be localized on an electroencephalogram of a parenchymal cyst or granuloma.

Table 71.2 Diagnostic criteria.

Absolute
Histological demonstration of parasite
Fundoscopic visualization of parasite
Cystic lesions with scolex on CT or MRI
Major
Lesions suggestive of neurocysticercosis on CT or MRI
Positive anticysticercal antibodies in serum or CSF
Calcifications on plain X-rays of thigh
Minor
Subcutaneous nodules
Clinical manifestations suggestive of cysticercosis
Disappearance of brain lesions with anticysticercal therapy
Epidemiological
Immigration from or living in endemic area
Travel to endemic area
Household contact with *Taenia solium* infection

Source: see ref. 201.

Table 71.3 Degrees of certainty for diagnosis: necessary criterion/criteria.

Definitive diagnosis
One absolute
Two major
One major, two minor and one epidemiological
Probable diagnosis
One major and two minor
One major, one minor and one epidemiological
Three minor and one epidemiological
Possible diagnosis
One major
Two minor
One minor and one epidemiological

Source: see ref. 201.

Giant convexity NCC cysts have frequently been treated surgically because of a misdiagnosis as arachnoid cysts or subdural haemorrhages on CT scans. Surgical intervention was advocated for subarachnoid cysts owing to poor CSF penetration of praziquantel and its lack of effect on these cysts [204], but reports since 1990 describe successful treatment of subarachnoid cysts with albendazole [205]. Although surgery may still be indicated for subarachnoid cysts refractory to albendazole, anticysticercal therapy is now the initial treatment of choice. Some lesions, however, still require surgical resection as first-line treatment; cysts adjacent to blood vessels and cranial nerves can cause an intense inflammatory reaction in response to cysticidal drugs, hence cysts in the parasellar region may cause optichiasmatic arachnoiditis and endarteritis of the supraclinoid internal carotid artery (leading to occlusion), and complex cysts within the Sylvian fissure may occlude the middle cerebral artery [206]. Skull base cysts should be treated surgically if there is symptomatic brainstem compression.

Surgical resection has been suggested as the treatment of choice for intraventricular lesions by several authors [207]; this is based on evidence of cases of sudden death related to CSF obstruction. Although standard open procedures provide acceptable access to most cysts, recent advances in neuroendoscopy have made removal of freely mobile, lateral and third ventricle cysts preferable to open craniotomy [208]. Cysts within the fourth ventricle may be associated with hydrocephalus and this should be treated before any decision is made regarding the cyst [207]. Excision may be warranted owing to potential cyst expansion, with brainstem compression, cyst migration or formation of granular ependymitis. Two surgical series showed good or excellent clinical outcomes in 81% and 71% of patients, with 15% and 26% morbidity, respectively [209,210]. A study of 10 patients treated with praziquantel and albendazole showed complete disappearance of 80% of fourth ventricular cysts. Of the other two cysts, one decreased significantly in size and the other remained unchanged. Six out of the 10 patients presented with hydrocephalus and underwent shunting before anticysticercal therapy [211].

A paper describing the experience of eight patients with NCC in the UK has demonstrated the value of a general conservative approach to treatment [177] and the development of a useful management protocol, in part based on the diagnostic criteria of Del Brutto *et al.* [201]. Seven of these patients presented with epilepsy and single or multiple small enhancing parenchymal lesions and one with hydrocephalus caused by a midbrain lesion. One lesion was stereotactically excised but five other lesions spontaneously resolved with patients receiving expectant management and AED therapy. Two patients with multiple lesions were free of active infection. The authors' view was that small cortical granulomas should not be biopsied or removed because the parasite is dying and will disappear spontaneously; this view is corroborated by other authors [193,201]. A conservative approach is also beneficial in that a stereotactic biopsy may be complicated by a haemorrhage owing to the toughness and mobility of the cysticercus and fragile blood vessels at the grey–white junction [212]. In the unlikely event of a cyst enlarging or causing increasing neurological deficit, treatment with anticysticercal therapy should be initiated in the first instance. However, if the lesion remains refractory to treatment, then surgery is inevitable [177]. In all cases in the series of eight described by Wadley *et al.* [177] a definitive diagnosis was made as per the diagnostic criteria outlined in Tables 62.2 and 62.3. During the course of treatment and observation of these patients, a coherent management strategy for patients presenting with epilepsy was produced (Fig. 71.6). It is recommended that for patients with a definitive or probable diagnosis after investigation, management should be expectant with AEDs alone and imaging should be repeated at 8–10 weeks. Surgery should be reserved for lesions that enlarge or persist despite additional anticysticercal treatment or when there is diagnostic uncertainty. This conservative approach is corroborated by other authors. Proano *et al.* [211] described their treatment of 33 patients with large subarachnoid cysticercal cysts, for whom the usual recommendation would be surgical treatment. All of the patients in this series improved with albendazole and dexamethasone at 59-month follow-up. In most patients, improvement was rapid after the initiation of treatment [211]. Reports such as these may change the standard of care for patients with NCC. NCC with a solitary or small number of cerebral lesions is a self-limiting infestation with a pattern of spontaneous resolution. Unnecessary surgery or therapy with potentially toxic drugs should be avoided.

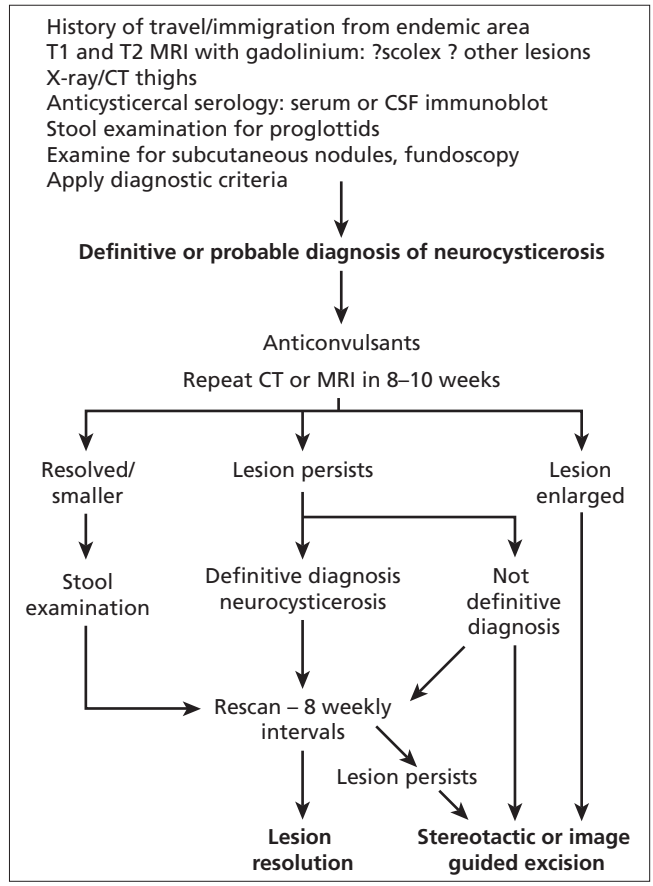


Fig. 71.6 Management protocol of a patient presenting with epilepsy and small enhancing lesions.

Cerebral tuberculoma

Background

Tuberculosis remains a major problem in developing countries and the incidence is rising in many industrialized countries owing to migration and HIV. Although the most common form of tuberculosis is pulmonary infection, CNS involvement is one of the most serious manifestations of the disease. The incidence of intracranial tuberculoma is decreasing, particularly in Western countries, and this is mainly due to the bacillus Calmette–Guérin (BCG) vaccination. In an autopsy study of intracranial space-occupying lesions (SOLs) conducted early in the 20th century (published in 1933), Garland and Armitage [213] found that tuberculomas represented 34% of all the SOLs, and in 1940 tuberculomas were said to account for 3.6% of 2190 brain tumours [214]. In 1959, Obrador [215] showed that cerebral tuberculoma accounted for 20–40% of all intracranial masses. In 1972, the incidence was put at 0.15% of 2200 intracranial masses [216]. In 1987, a study in Saudi Arabia showed that tuberculoma constitutes approximately 5% of intracranial SOLs [217], and a further report in 1993 estimated that cerebral tuberculoma in children constitutes 5–10% of intracranial SOLs in developing countries [218]. Reports of brain tuberculoma have appeared in the developed countries among immigrants [219] and patients with HIV [220]. In a recent study of 455 HIV cases in India, 23 patients had new-onset seizures, and 13% of these were caused by cerebral tuberculoma [2]. Gulati *et al.* studied 170 Indian children with chronic seizures and a high index of suspicion of an underlying SOL, and MRI indicated tuberculoma in 64 of them [221]. A study by Rebai *et al.* [222] over 16 years examined 1015 cases of intracranial SOLs; 24 of these (2.4%) were found to be tuberculomas. Because of their rarity, tuberculomas are not always considered in the differential diagnosis of intracranial SOLs. Furthermore, the exact pathophysiology is still not clear, partly because of the impossibility of reproducing tuberculoma in animals.

Tuberculomas are typically firm, lobulated masses of granulomatous inflammation with central caseous necrosis up to several centimetres in diameter and walled off by fibrous tissue. Lesions can occur within the cerebellum but are most common in the cerebral hemispheres [222].

Diagnosis

The diagnosis of intracranial tuberculoma should rest on the proper integration of data from clinical manifestations, CSF analysis and neuroimaging studies [223]. Tuberculoma should be distinguished from tuberculous meningitis, although the two may coexist. Rupture of a parenchymal lesion into the CSF has been implicated in the formation of tuberculous meningitis [224].

Computed tomography and MRI were directly compared in a study of six patients [223]. Although both were equally sensitive in visualizing the intracranial tuberculoma in every patient, MRI was superior in demonstrating the extent and maturity of the lesion, especially for brainstem lesions. Nevertheless, the diagnostic role for MRI in intracranial tuberculomas is limited by its inability to differentiate between other infections or neoplasms. In the developing world, CT remains the radiological investigation of choice.

The identification of a target lesion on an enhanced CT scan is characteristic of tuberculoma, although it is also seen with toxoplasmosis. It is difficult to distinguish tuberculoma from NCC; the criteria for differentiation using CT were described by Rajshekar *et al.* [193], and this difficulty was also highlighted by Garg *et al.* [225], who described an NCC-like presentation in a case of CNS tuberculosis in India. A clinical picture of seizures, multiple non-tender subcutaneous nodules and multiple ring-enhancing lesions on brain CT, was seen in a patient in an area endemic for NCC. Serological tests and histopathology established tuberculosis as the cause.

Diagnosis is further complicated by the fact that many patients with tuberculoma have no preceding history of tuberculosis infection. In the series of Rebai *et al.* [222], only 29% of patients with tuberculoma had a history of tuberculous infection (although bacterial examination is not conclusive even if negative). Although solitary lesions are generally more common, the diagnosis has been stated to be easier in cases with multiple intracerebral lesions. Boucetta *et al.* [226] reported solitary lesions in 84% of their patients, and 19% of the patients in the series by Rodat *et al.* [227] had multiple tuberculomas.

Management

Historically, tuberculomas were managed surgically; however, the development of antituberculous chemotherapy has reversed this [228]. Surgery may still be indicated, if the diagnosis is in doubt, for intractable epilepsy or mass effect causing intracranial hypertension, and there are reports of paradoxical expansion of intracranial tuberculomas during chemotherapy [229]. Two years of medical therapy is deemed suitable prior to consideration of epilepsy surgery; occasional debilitating seizures may warrant earlier referral. Delay in definitive treatment can be devastating; in one patient [230], rupture of the parenchymal lesion into the CSF led to the fulminating and fatal intracranial spread of the tuberculosis. Conversely, lesions involving eloquent cortex are likely to lead to increased neurological morbidity, and it may be prudent in such cases to defer surgical referral. It has been argued that, if diagnosis is likely, a trial of antituberculous therapy should be begun without biopsy confirmation [209]. Others [229] favour early open brain biopsy as soon as intracranial tuberculoma is suspected, especially in rapidly progressing cases. Primary medical treatment with frequent monitoring is reserved for lesions in the pons and brainstem or for multiple forms that are impossible to approach surgically. Cerebral tuberculomas with co-existent extracranial disease should also have primary medical treatment. Cerebral tuberculomas usually decrease in size within 8 weeks of starting medical therapy and this is accompanied by improved neurological status. Diagnosis should be reviewed if the anticipated improvement in clinical condition and radiological appearance is not forthcoming [217]. Furthermore, corticosteroids should be avoided during the therapeutic trial as regression of an underlying lymphoma can be misinterpreted as a favourable response to antituberculous chemotherapy [231]. With early diagnosis and a balanced combination of surgical and medical management, cerebral tuberculoma is curable.

Hydatid disease

Background

Echinococcus is a parasite that is endemic to Eastern Europe, the Middle East, Argentina, Chile, Uruguay, South Africa, Australia

and New Zealand, although its distribution is worldwide. Hydatid (meaning 'drop of water') describes the fluid-filled cysts created by the parasite. The dog tapeworm, *Echinococcus granulosus*, accounts for the majority of hydatid disease and tends to cause cystic brain lesions. *E. multilocularis* is a rarer cause of hydatid disease, which produces alveolar brain lesions. Domesticated dogs are the definitive hosts for the parasite and acquire the tapeworm when ingesting parasite-infested viscera of sheep and cattle (the intermediate host). The adult worm resides in the intestine and has a lifespan of approximately 6 months. Sheep typically become intermediate hosts by ingesting parasite ova in dog faeces; humans may interrupt the cycle, becoming intermediate hosts also by ingesting parasite ova originating in dog faeces. On ingestion of the ova, the larvae hatch and penetrate the intestinal mucosa. Haematogenous dissemination leads to the formation of cysts in the brain and spinal cord.

Two different histological types of cerebral hydatid cyst have been described: embryonal (primary) and scolical (metastatic or secondary) [191]. Primary cerebral hydatidosis is caused by embryos that escape filtration by the liver and lungs and become implanted in the brain parenchyma. Owing to their embryonal origin, primary cysts are usually fertile, as they contain many scolices. Primary cysts are almost always solitary, reports of multiple primary cerebral hydatid cysts being very rare [230]. In contrast, secondary metastatic cerebral hydatid cysts originate from infertile scolices of ruptured fertile cysts and are therefore usually infertile. Cerebral cysts have a variable rate of growth of 1–5 cm/year but may expand relatively quickly due to the immunological quiescence of the brain and a scant fibroblastic response. Cystic expansion may lead to compression and necrosis of surrounding tissues. In a series of 120 patients, 6% of the cysts measured between 6 and 10 cm in diameter and six cysts measured more than 20 cm in diameter [232].

Diagnosis

Cerebral hydatid cysts can occur at any age, but are most common in children. In a series of 155 cases, 117 were children, with a mean age of 7.2 years and a slight male predominance [233]. The most common mode of presentation in children is raised intracranial pressure. In adults, focal motor deficits are the more common, with signs of raised intracranial pressure occurring later. The presenting symptoms and signs in reducing order of frequency in a group of 120 patients with cerebral hydatid disease were headache (80%), papilloedema (74%), vomiting (70%), hemiparesis (60%), facial paresis (42%), cerebellar dysfunction (42%), hemianopia (40%), seizures (36%), reduced visual acuity (35%), ataxia (20%), somnolence (20%) and speech disturbance (15%) [232].

Laboratory tests are not particularly helpful in establishing the diagnosis. Serological tests can be useful, and ELISA, latex fixation and haemagglutination are acceptably sensitive and specific; however, all are limited by cross-reactivity with *Taeniidae solium* and are not sufficient on their own to establish the diagnosis [234]. Immunoglobulin G (IgG) ELISA, however, is useful as it has a sensitivity of up to 94% and a specificity of up to 99%. Radiological examination is important; lesions can remain undetected on CT scanning when they are visible on MRI [235]. Lack of rim enhancement, absence of perilesional oedema and, occasionally, calcification of the cyst rim are seen. Studies have shown significant variability in CT and MRI features of these cysts, such as irregularity in shape and contour of the cyst wall, cyst contents isodense to brain, heterogeneity of cyst fluid density, enhancement of the rim, surrounding brain oedema and globular calcification of the cyst margin [236].

Differential diagnosis should include NCC, arachnoid cysts, cerebral abscess and cystic tumours, such as metastasis, haemangioblastoma and glioma. Features distinguishing NCC from a hydatid cyst include size of the lesion and the presence of calcifications. Most parenchymal cysts of NCC are less than 2 cm in diameter, whereas hydatid cysts are usually much larger. Calcified parenchymal granulomas are seen in 58% of NCC patients, whereas calcification of the cyst rim is seen in fewer than 20% of hydatid cyst cases [232]. Brain abscesses and many neoplasms may produce perilesional oedema and also demonstrate significant contrast enhancement and a case report of solid cerebral *Echinococcus* mimicking primary brain tumour has been described [237]. Arachnoid cysts are probably the most difficult lesions to differentiate from hydatid cysts; arachnoid cysts are typically less spherical than hydatid cysts, but this is not always the case.

Management

Establishing the diagnosis preoperatively is crucial, as this guides surgical technique. Resective surgery remains the primary treatment of the disease. The standard surgical technique used for excision of large tumours containing cysts, i.e. aspiration and deflation of the cyst before resection of the tumour itself, is absolutely contraindicated as this risks turning a potentially curable condition into a chronic ongoing disease characterized by repetitive cyst recurrence. If the primary cyst ruptures, the enclosed protoscolices spill into the surrounding parenchyma and each protoscolex is able to transform into a secondary cyst. Most hydatid cysts are located at the grey–white matter junction as a result of haematogenous spread, typically in the distribution of the middle cerebral arteries. However, deep brain or intraventricular lesions are virtually impossible to resect without them rupturing. One accepted method of cyst removal is the Dowling technique [238]. Rather than using sharp dissection, this method relies on gravity to deliver the cyst from the surrounding brain. The patient is positioned on the operating table such that the cyst is in a dependent position. A large bone and dural flap are reflected and a cortical incision is made over the thinnest area overlying the cyst. Saline irrigation is used to dissect a tissue plane between the cyst and surrounding parenchyma. If the lesion is deep to the cortical surface and complete resection is not feasible, careful cyst aspiration is recommended, with hypertonic saline or silver nitrate solution used to destroy protoscolices [238].

The antihelminthic drug albendazole is effective in the treatment of cerebral *Echinococcus* [239]. Its success in a limited number of patients suggests that it may be preferred to surgery in certain clinical settings. Albendazole can achieve cyst concentrations of up to 40% of serum concentrations, causing disruption of the cyst wall and death of the protoscolices. It could be used adjunctively to shrink large superficial cortical cysts, as this would facilitate removal and reduce risk of rupture during resective surgery. Furthermore, albendazole prevents the formation of secondary cysts in case of inadvertent rupture. For cysts in eloquent brain or those in deep areas, the risks of surgery may be substantial. In such cases, albendazole alone may be able to resolve the cyst and obviate the need for surgery. It is also useful

in the treatment of secondary cysts that recur after surgery at the original site. Hepatotoxicity is a major limitation of albendazole use and hepatic enzyme levels must be monitored closely. Surgery remains the best option for large lesions; it produces immediate clinical improvement, unlike drug therapy, through which cyst resolution may take months or years.

Cyst rupture during attempted resection significantly affects prognosis. This is because the cyst contents are highly antigenic and rupture may lead to severe anaphylaxis with circulatory shock and death [240,241]. In a 1992 study, 10 (24%) of 41 patients in whom cyst rupture occurred during surgery died within 36 days of surgery. However, no deaths occurred among the 79 patients without cyst rupture.

Cyst rupture has also been seen to occur spontaneously in some patients. A rapid clinical deterioration is seen and severe pericystic oedema is seen on CT. This is a surgical emergency: removal of cyst contents must be carried out immediately, with copious saline irrigation and administration of antihelminthic drugs.

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72 Surgery of Developmental Anomalies Causing Epilepsy

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Introduction

Malformations of cortical development (MCDs) consist of a group of brain developmental anomalies (for a comprehensive discussion and classification scheme, see ref. 1). These disorders were originally named according to their gross anatomical appearances: polymicrogyria (PMG), schizencephaly, lissencephaly (LIS), hemimegalencephaly, grey matter heterotopia and focal cortical dysplasia (FCD). Various classifications were introduced with different emphasis. For example, the classification by Barkovich *et al*. in 1996 [2] subdivided these disorders based mostly on stages of development: disorders of neuronal and glial proliferation, abnormal neuronal migration and/or cortical organization. Further categorization could be made based on location, extent of disease and histological findings. The classification by Palmini *et al*. in 2004 [3] was exclusively based on histology. More recently, information from genetics, molecular biology and neuroimaging has been included in some of the newer classification schemes [1].

This chapter will consider surgical treatment of refractory epilepsy due to various types of MCD. Tumours such as dysembryoplastic neuroepithelial tumour and ganglioglioma were sometimes labelled as 'developmental' and were categorized under MCD in some classification schemes, but this is the subject of Chapter 70 and will not be discussed here. The most common and distinct disorders will be considered separately, highlighting surgical results. A particular emphasis is placed on FCD, which is the most common type of MCD diagnosed in surgical series. Advancement in various presurgical assessments, including imaging technique and EEG monitoring, will be discussed here briefly although covered elsewhere in detail (Chapters 60–65).

Epidemiology

The prevalence of MCD in the general population and in various patient groups is not precisely known, the reason being that the presentation of MCD could vary widely. Patients with mild forms of MCD (i.e. FCD) might have no symptoms at all or mild symptoms that were undiagnosed. In an autopsy series of 7374 brains of healthy individuals that was published in the early 1990s, FCD was found in 1.7% of subjects [4]. In the era of modern imaging, however, more MCD disorders have been identified in asymptomatic subjects. In a report of 100 consecutive patients with a neuroimaging diagnosis of MCD it was found that 33 presented with a normal neurological examination, 61 presented with partial epileptic syndromes and 13 with secondary generalized syndrome [5]. In patients with severe signs and symptoms, i.e. developmental delay and/or epilepsy, increased incidence and severity of MCD might be expected. For example, in a series of 98 mentally retarded children with epilepsy, 60% were found to have generalized MCD on MRI [6].

The prevalence of MCD in epilepsy patients is estimated via surgical series or imaging. In a study published in 1995, 12% of 341 patients with refractory epilepsy had MRI diagnoses of MCD [7]. Before the era of imaging, 3% of patients who underwent surgery at Montreal Neurological Institute for epilepsy were found to have some type of MCD (YGC's experience). A case series of 133 consecutive resections for extratemporal intractable epilepsy at Cleveland Clinic established MCD as the histological diagnosis in 37.6% of cases [8]. MCD is particularly common in the paediatric epilepsy surgery population. In the paediatric UCLA surgical cohort from 1986 to 2005, MCD was identified in 45.5% of operated patients from age 2 months to 19 years [9]. In another study published in 1998 based on patients under 20 years old, MCD was found in 31 out of 120 patients (26%) [10]. Moreover, the diagnosis of MCD was found to be an independent prognostic factor for seizure intractability [11], and patients with MCD often have drug-resistant epilepsies [12].

Selection of surgical candidates

Although Taylor *et al*. [13] demonstrated more than 30 years ago that intractable epilepsy associated with cortical dysplasia could be successfully treated with surgery, surgery for MCD was performed on a small scale with poor results. Palmini *et al*. in 1991 [14] reported on a series of 30 patients from the Montreal Neurological Institute; surgical outcome in the series was not optimal, with only 11% achieving a seizure-free outcome. This report and the demonstration in the early 1990s by the UCLA epilepsy programme that children with catastrophic epilepsy secondary to severe MCD, including hemimegalencephaly, could be successfully treated with surgery rekindled interest in MCD. Subsequently, several reports confirmed the findings of the UCLA group. Furthermore, improvement in imaging and surgical strategies for the management of this group of disorders led to better detection and dramatically improved surgical outcomes.

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Patients with drug-resistant intractable epilepsy are selected for surgical treatment. Infants with MCDs frequently have catastrophic epilepsy with heavy seizure burden and progressive developmental delay. The extent of reversibility of this delay has been the subject of several studies. All candidates with suspected MCDs should undergo an extensive presurgical evaluation that seeks to determine the presence and extent of the MCDs, the extent of the epileptogenic zone, and the relationship of the proposed resection to functional brain areas. This task is particularly complicated in children because of the presence of wide epileptogenic zones and the difficulty with localizing functional brain areas.

Presurgical evaluation: to determine the extent of the epileptogenic zone

The goal of presurgical evaluation is to determine the extent of the epileptogenic zone. The determination of the epileptogenic zone relies on data obtained from clinical examination, seizure semiology, imaging and electrophysiology. An essential first step is a demonstration of a MCD by MRI. Although the epileptogenic zone frequently extends beyond the MRI abnormality when demonstrated, the finding of an abnormality on the MRI greatly facilitates the presurgical evaluation and is considered an essential first step in the delineation of the extent of the epileptogenic zone. However, in a significant number of cases MRI is negative despite the acquisition of the sophisticated sequences and techniques described below. These patients are still considered for surgery with a heavier reliance on invasive electrodes.

History, physical examination and seizure semiology

The importance of careful history, physical examination and seizure semiology cannot be understated. In the presence of a family history of seizures, genetic counselling and testing is recommended. This is common in familial polymicrogyrias, schizencephaly and periventricular nodular heterotopia. Febrile convulsions are associated with hippocampal sclerosis and in the presence of a MCD a dual pathology should be considered [15]. Neurocutaneous syndromes associated with MCDs are noted on physical examination. Paresis is indicative of involvement of the central area. Neuropsychology testing is performed to establish a baseline; a developmental delay ranging from mild to severe is common.

Seizure semiology is related to the location of the epileptogenic zone; however, infantile spasms can be generated in children by MCDs in any brain location – a higher incidence of left hemispheric lesions associated with infantile spasms has been reported [16], although this has not been our experience. In infants, false localizing signs are related to the immaturity of the white matter tracts.

The clinical characteristics of 120 patients with a focal cortical dysplasia have been reported by Fauser *et al.* [17]. Seizure onset was before the age of 5 years in the majority of patients, although it could occur until the age of 60 years. Patients with mild FCD (type Ia of Palmini) had significantly later epilepsy onset. Age of seizure onset was unrelated to FCD localization; a change in seizure semiology occurred between the ages of 1 and 14 years – 17% of patients showed transient responsiveness to AED either at initial treatment (50%) or later (50%).

Auras carry a very important localizing value and together with seizure semiology contribute to developing a hypothesis on the location of the epileptogenic zone. The hypothesis is then confirmed by MRI and other presurgical tools. A discrepancy between semiology and imaging is suggestive of dual pathology. Multiple seizure generators are noted in dual pathology, with rapid seizure propagation. This condition is usually associated with poor seizure outcome. Status epilepticus is noted in 15% of patients.

Role of imaging

MRI

The critical importance of MRI in the diagnosis of MCD and treatment of epilepsy due to MCD has already been noted. It has a direct impact on the establishment of diagnosis, which in turn influences the surgeon's and clinician's decisions on treatment selections. Furthermore, a recent systematic review of the literature confirmed that an abnormal MRI was among the strongest predictors of seizure outcome after surgery [18].

The MRI evaluation is age dependent and is modified depending on the extent of the brain myelination. Before the age of 10 months, heavily T2-weighted spin-echo images are obtained. In older individuals, 1–2 mm thin section, T1- and T2-weighted images are necessary. There are expert recommendations on MRI acquisition techniques and sequences for MCD in general, with a particular emphasis on the importance of fluid attenuation inversion recovery and T2-weighted sequences [19]. Many reports have described typical MRI features of FCD: gyration anomalies, focal thickenings of the cortex, blurring of the grey–white junction, and abnormal cortical and subcortical signal intensity [20,21].

Malformations of cortical development lead frequently to abnormal gyral and sulcal development of the brain. Therefore, knowledge of the normal sulcal anatomy is essential for the detection of subtle anomalies. If the initial MRI investigation is negative, subtle anomalies can be detected by using advanced techniques that include phased-array surface coils, three-dimensional curvilinear reconstruction with postprocessing morphometry [22,23]. MRI (3-tesla) has demonstrated an increased capability in detection of dysplasia, particularly of the transmantle type.

Magnetic resonance spectroscopy

The sensitivity and specificity of magnetic resonance spectroscopy in the detection of MCD has not been assessed in a systematic fashion. Previously, spectroscopy has suffered from a limited spatial resolution and limited sampling of the region of interest. Several studies have demonstrated a decrease in NAA/Cho ratio and NAA/Cr ratio in FCD [15,24,25]. These findings are nonspecific for cortical dysplasia and have been reported in temporal lobe epilepsy [26,27]. In general, the extent of spectroscopic abnormality is larger than the structural imaging abnormality and the utility of magnetic resonance spectroscopy in MCD is being

assessed in patients whose initial MRI yielded unremarkable results.

Tractography and diffusion tensor imaging

Abnormalities of proliferation, migration and layering theoretically should result in anomalies of the white matter tracts of the brain. Diffusion tensor imaging (DTI) techniques have demonstrated increased diffusion in a high proportion of MCDs, and tractography has shown decreased and aberrant fibre connections with brain areas outside the structural abnormality. This technique is promising and contributes to a better assessment of the extent of the lesion. The abnormal white matter tracts associated with MCD could provide an explanation of the unusual propagation patterns and unexpected interactions between non-contiguous cortical and subcortical sites that has been reported by Duchowny [28,29] using subdural electrodes.

PET scanning

PET scanning has been used in the detection of MCDs before the development of high-resolution MRI [30]. The FDG-PET hypometabolism demonstrated reflects the functional deficit zones, therefore it includes but is wider than the epileptogenic zone [31]. PET scanning can be very useful in MRI-negative temporal and extratemporal cases [32,33]. Several new ligands are expanding the applications of PET scanning.

[^{11}C]-Flumazenil (FMZ) PET binding with the GABA receptor and [^{11}C]-α-methyl-L-tryptophan (AMT) improves the visualization of neocortical epilepsy in MRI-negative patients [34–41]. Decreased flumazenil binding appears to correlate better with the epileptogenic zone than glucose hypometabolism. FMZ may demonstrate secondary epileptogenic foci remote from the primary epileptogenic zone. Other ligands are being developed (for review see ref. 42).

SPECT scanning

Ictal SPECT scanning with substraction techniques appears as a highly sensitive method in the presurgical evaluation of a patient with cortical dysplasias. It is especially useful in MRI-negative cases, ranging from 56% [43] to 80%) [44]. The yield depends on early administration of the radiotracer at the onset of the seizure followed by sophisticated analysis methods [45–47]. These requirements have limited the use of ictal SPECT to centres which have developed a specific expertise in its administration and data analysis.

EEG/fMRI

EEG/fMRI is a new investigation modality that combines the high temporal resolution of EEG with the exquisite anatomical resolution of MRI. This allows a precise localization of the cortical and subcortical sources of paroxysmal EEG changes. Although reports of this technique are preliminary and have not been applied on a large scale to the study of cortical dysplasia, recent reports have provided important insights into the epileptogenicity of MCDs and interaction between MCD and surrounding cerebral structures in the genesis of epileptic activity [48–53]. These findings are discussed in conjunction with the role of invasive electrodes.

Role of electrophysiology

Long-term electroencephalography monitoring

The value of surface electroencephalography in the presurgical evaluation of MCD has not been investigated. Dubeau and Palmini [54] reported that two-thirds of patients with FCD have lateralized interictal findings on EEG corresponding to the localization of the malformation. However, bilateral independent interictal activity is not infrequent in children and should not lead to exclusion from presurgical evaluation. Widdess-Walsh [55], in a series of 48 patients, showed that 64% of patients had a regional surface ictal EEG pattern, 25% had a lateralized onset, and 11% had a non-localizable ictal pattern. Foldvary *et al*. [56] demonstrated that false localization occurs in high frequency in mesial frontal (75%) and mesial parieto-occipital locations (36%). Ictal beta rhythms, when present, are an excellent prognostic factor in frontal lobe epilepsy [57].

Invasive recordings

The value of invasive electroencephalography recordings in the delineation of the extent of the epileptogenic zone has not been completely settled. In most centres, some form of electroencephalography recording is used to delineate the extent of resection. We will discuss the benefits and limitations of each method.

Electrocorticography

In 1991 Palmini *et al*. [14] described distinctive electrocorticography (EcoG) patterns over dysplastic cortex consisting of frequent ictal trains of continuous spikes. This pattern was present in 67% of patients and correlated well with the anatomical extent of the lesion. This EEG pattern was not present in controlled patients and was more restricted than diffuse interictal discharges recorded in 82% of patients. These findings were confirmed by several authors. Ferrier *et al*. [58] demonstrated that the continuous ECOG spiking activity of Palmini was also noted in 12% of patients with glioneural tumours. In their series, only 55% of patients with FCD demonstrated continuous spiking. The discharge pattern did not correlate with the presence or absence of balloon cells on pathology. These studies and others demonstrate that, when present, epileptiform discharges can delineate the extent of the epileptogenic zone and provide the surgeon with an excellent tool in determining the extent of resection. Their persistence post resection would indicate residual dysplastic epileptogenic tissue and, therefore, a poor outcome. However, it has been our experience that EcoG is non-informative in approximately 50% of patients with FCD.

Invasive electrodes

Two types of invasive electrodes are used in the investigation of MCD: subdural grid electrodes and stereo EEG using depth electrodes. These both allow mapping of cortical function, therefore correlating ictal discharges with adjacent cortical function. The choice of electrodes is influenced by the centre preference and the location of the malformation. Periventricular nodular dysplasias, given their location, are more amenable to depth electrode investigation. At times, a combination of subdural and depth electrodes is indicated.

Subdural electrodes The efficacy of subdural electrodes in detecting an ictal onset area in MCD is still controversial. Despite the widespread use of these electrodes in MCD, results have not been adequately reported. A study from the Cleveland Clinic on 48 patients who received subdural electrodes demonstrated a diffuse ictal onset zone in 35% of the patients despite wide coverage. An ictal onset involving the edge of the subdural electrode was noted 49% of the time, and two or more separate ictal onset areas were detected in 41% of patients. Complete resection of the ictal onset zone led to a 65% seizure-free outcome. Incomplete resection of the ictal onset zone was associated with an 8% seizure-free outcome [55].

Recent advances in EEG are providing clues that could improve the ability of invasive recordings to demonstrate the ictal onset zone in some patients with MCD. Classical recording techniques have used a 200-Hz sampling rate and filtered EEG signal to around 70 Hz. High-frequency oscillation (HFO) above 70 Hz, although reported in animal models [59] and in patients with FCDs, was not initially perceived as clinically relevant [60]. Several centres have now demonstrated that HFO can be recorded using subdural and depth electrodes and that their depiction appears to approximate closely with the ictal onset area [61]. In 2007 Ochi *et al*. [62] reported that resection of areas associated with ictal HFO resulted in good surgical seizure-free outcomes [62].

Depth electrodes and SEEG The results of depth electrode investigations of the major types of MCD have been reported and have improved our understanding of the epileptogenicity of these malformations [49,63–70]. Depth electrodes appear to be superior to subdural electrodes in detecting a focal ictal onset area, with 93% efficacy in a large series [63]. This is explained by the ability of depth electrodes to sample tissue that is inaccessible to subdural electrode investigation.

Intralesional SEEG recordings from focal cortical dysplasia, in Taylor type and also non-Taylor type, have demonstrated a characteristic interictal pattern of repetitive and rhythmic spikes and polyspike waves [64]. This therefore confirms the high intrinsic epileptogenicity of FCDs noted in Palmini's reports using EcoG.

Depth electrode investigations are also particularly informative in periventricular nodular heterotopias, and several authors consider them to be necessary before resective surgery [65]. Epileptogenicity in these lesions involves a complex network that includes the ectopic grey matter, the overlying cortex and, not infrequently, the hippocampal formation. Identifying a focal generator is a good predictor for resective surgery in this MCD subtype.

Electrode recordings from nodular heterotopias have shown independent epileptiform discharges occurring in the heterotopia and the overlying cortex. In the temporal lobe, epileptiform activity can come from heterotopia, the overlying cortex and/or mesial temporal structures independently. In some cases, activations are recorded from the heterotopia and surrounding cortex with concomitant activation of a distant cortical area that bears no clear relationship to the lesion. In band heterotopias, wide activation from both the lesion and surrounding cortex were noted, confirming the diffuse nature of this lesion. Interestingly, fMRI activation rarely involved the entire heterotopia but was confined to restricted areas within the lesion [67]. These data appear to contradict findings using invasive recordings using SEEG [65].

Focal polymicrogyria has also been investigated using depth electrodes. In this pathology, the ictal onset zone is frequently outside the polymicrogyric cortex and involves the mesial temporal structures. As previously described by Silbergeld and Miller [71], wide resections that include the epileptogenic zone and the polymicrogyric cortex, when possible, are recommended [66].

EEG/fMRI has clarified the epileptogenicity of polymicrogyria. Previously, invasive recordings had failed to confirm intrinsic epileptogenicity within PMG. fMRI activation was noted within the polymicrogyria in 65% of patients. It also involved a focal area within the PMG in 61% of patients [67].

Magnetoencephalography

Magnetoencephalography (MEG) offers several advantages over EEG in the determination of the extent of the epileptogenic zone and its relationship to eloquent cortex in MCD. As MCDs are frequently deep and assume complex configurations, MEG-source modelling allows better determination of the location and time activities of the dysplastic neurones compared with EEG. It also allows the display of these activities on MRI imaging facilitation the surgical planning [72].

Several studies using MEG have confirmed intrinsic epileptogenicity of FCD previously reported by surface EEG recordings [73–75]. In one study comparing MEG with invasive EEG recordings in patients with cortical dysplasia it was revealed that MEG and EEG are complementary, as EEG is mostly sensitive to superficial currents and MEG detects preferentially tangential current within fissures [76].

In MRI-negative patients with cortical dysplasia, MEG investigation reveals subtle abnormalities that are verifiable pathologically [77].

Magnetoencephalography plays a role in the localization of essential cortex. Localization of the central sulcus is possible with an accuracy of a few millimetres [78]. In addition, various language paradigms allow mapping of speech areas [77,79–81].

Magnetoencephalography therefore can add critical information to the decision-making in the presurgical assessment of patients with MCD.

Surgical outcome

Surgical outcome in grey matter heterotopia

Heterotopia of grey matter is classified into three types: laminar, band and nodular. Nodular heterotopia is further classified according to the location: periventricular or subcortical. Heterotopia may be focal or multifocal, and it may or may not be associated with other cortical malformations.

Not surprisingly, patients with nodular heterotopia without other cortical malformations had a more benign clinical course. Seizure type tended to be partial, with onset in early adulthood, and susceptible to antiepileptic drug treatment, and the number of seizures decreased with time [68,82]. Occasionally, if the heterotopia is unilateral and localized, and its epileptogenicity confirmed (usually by invasive monitoring), seizure-free outcome may be obtained after surgery (9 out of 16 patients from refs 65 and 83 combined). In these cases, resection of additional areas adja-

cent to the heterotopic nodules and/or other remote epileptogenic area was almost always necessary.

A bigger proportion of patients, however, had heterotopias that were either diffuse or were associated with other MCD disorders, and surgical resection was often not an option. The most frequently associated MCD disorder was mesial temporal sclerosis [84,85]. These patients had a higher prevalence of epilepsy, developmental delay and neurological deficit [82,86]. When they did undergo resection, whether it was directed at the heterotopia or the mesial temporal sclerosis, the result was generally poor [87]. Stereotactic radiosurgery for heterotopia has been considered as a surgical option but a literature search did not reveal any published references.

Surgical outcome in lissencephaly

Lissencephaly consists of a paucity of gyri and sulci. Depending on the extent of involvement, agyria and pachygyria are also included in this disorder. Correspondingly, clinical manifestations are also quite variable. A PubMed search did not identify surgical series based solely on patients with lissencephaly. In case series on corpus callosotomy, some patients, whose underlying abnormality were bilateral lissencephaly with clinical manifestations of drop attacks and generalized tonic seizure, did benefit from surgical intervention [88,89].

Surgical outcome in hemimegalencephaly

Hemimegalencephaly arises from a global abnormal proliferation of neurones and glia that tends to affect an entire hemisphere. Traditionally, hemimegalencephaly is treated with hemispherectomy with limited success. An excellent review of recent surgical series was published by Di Rocco *et al.* [90]. In a total of 78 patients published in 11 reports since 1994, 31 patients achieved Engel class I outcome. There was a general improvement in cognitive and psychomotor development. Surgical technique included anatomical hemispherectomy or hemicorticectomy or functional techniques that all seemed to be equally efficacious. The authors speculated that the lack of complete success was due to the possibility of disease in the 'healthy' hemisphere that escaped imaging detection, and the difficulties in performing the surgery due to the severe anatomical distortion. However, surgical complications, including hydrocephalus, infection, fever and death, could affect up to 50% of patients.

Surgical outcome in polymicrogyria, schizencephaly and porencephaly

Polymicrogyria consists of abnormally small gyri that could be focal, bilateral, perisylvian or diffuse. Histologically, there is a decreased number of neurones, which is most pronounced at layer V. The normal-appearing neurones in adjacent layers suggest that the proliferation and migration of the neurones are grossly intact, and it is the late process of cortical organization that is interrupted [1]. Thus, it is generally believed that polymicrogyria is an acquired lesion due to intrauterine insults, which is mimicked by the rat freeze lesion model.

There are few case reports of surgical treatment of polymicrogyria and no surgical series were identified [91–93]. All emphasized that the malformation was more extensive than that which was indicated by MRI.

Schizencephaly is characterized by a cleft extending through the thickness of the cortex lined by polymicrogyria; therefore, it is often included in the same category of cortical organization disorder as polymicrogyria [1]. One of the difficulties associated with these cases comes from the fact that the cortex within the cleft is not easily accessible for recording. Surgical techniques used in case reports include partial or total resection of the walls of schizencephalic cleft, resection of surrounding regions and multiple subpial transections of the cleft wall [71, 94–96].

Surgical outcomes in porencephaly

Continuing with the theme of prenatal and perinatal insult, porencephaly is sometimes associated with epilepsy. Patients usually present with hemiparesis and intellectual impairment in addition to intractable epilepsy [97]. Hemispherectomy of various degrees is often the only surgical option, but in selected cases focused cortical resection is possible [98].

Surgical outcome in focal cortical dysplasia

Focal cortical dysplasia is localized by definition and therefore affords the possibility of surgical resection as a treatment option. As a result, many more patients with FCD than with other types of MCD have undergone surgery. A greater availability of surgical specimens enables histological, molecular and genetic studies, which then make possible correlations with clinical and imaging findings.

Classifications

The term 'cortical dysplasia' was first proposed in 1971 by Taylor *et al*. [13] to describe the histology of epileptogenic neocortex. In the simplest terms, FCD is the 'subtype of MCD in which the developmental abnormality is strictly or mostly intracortical' [3]. Additional subdivisions include the following: type 1A, cortical architectural abnormalities; type 1B, architectural abnormalities with giant cells (meganeurones), but no dysmorphic neurones or balloon cells; type 2A, dysmorphic neurones in the setting of architectural abnormalities; and type 2B, the presence of balloon cells intermixed with dysmorphic neurones in the setting of architectural abnormalities [3]. This is the most widely used histological classification today.

The majority of FCD patients experience onset of epilepsy by 5 years of age; however, seizure onset can also occur in the second or third decade. Patients can present with generalized or partial seizure or in status epilepticus. Even although some show transient responsiveness to antiepileptic drug therapy, this group of patients often has intractable seizures [17]. Most studies found that the presence of dysmorphic and balloon cells was positively correlated with younger age of seizure onset, more frequent seizures and more severe cognitive disability [17,99,100]. However, the correlation between histology and surgical outcome is much less well defined (see below).

Imaging

Approximately 90% of patients who were selected for surgery and had a histologically confirmed FCD had an identifiable lesion on preoperative MRI (see below). This percentage did not reflect the sensitivity of MRI at detecting FCD, but merely indicated that patients with normal MRI were less likely to be offered surgery.

Two clinically relevant questions can be asked concerning the role of MRI. First, can one accurately predict histological subtypes based on MRI findings, which may provide prognostic information and influence patient management, without subjecting patients to surgical biopsy or resection? Few studies directly answered this question. Studies by Colombo *et al*. [101] and Matsuda *et al*. [102] showed that even although different histological subtypes can be distinguished with MRI to some extent, enough overlap existed such that the clinical usefulness of this information was limited [101,102]. A second relevant question concerns whether or not MRI displays the real extent of the cortical dysplasia. Because a significant proportion of patients who underwent complete resection per imaging criteria still suffer from seizures (see next section), the answer is probably 'no'. As MRI technique continues to advance, one would expect that more and more patients will be offered surgery and better outcome will be obtained, but there will always be a small number of patients whose lesions escape imaging and who will thus stimulate further technical progress.

Surgical outcome

Focal cortical dysplasia is by far the most common MCD identified in surgical specimens. The focal nature of the disease means that patients are more often selected for surgery than those with more diffuse types of MCD. We have reviewed surgical series based on patients who underwent resective surgery and whose histological diagnosis was focal cortical dysplasia [69,103–119]. All 18 series were published since 2000 and all with a follow-up period of at least 1 year. All patients had preoperative MRI with 1.5-T magnet or better. Studies were included only if seizure-free outcome was reported explicitly.

A total of 469 patients and their surgical outcome were available for review: 59.7% of patients (280 out of 469) achieved seizure-free status 1 year postoperatively. This rate of success does not differ between patients who were older than 18 years (60.3%) or younger (59.8%). Overall, 89.4% of the patients had a lesion that was detectable by MRI, but a considerable percentage of patients who had a normal preoperative MRI were seizure free after the surgery (20 out of 36).

The one variable that most significantly correlates with a seizure-free result was the extent of lesion resection. In total, 71 out of 87 patients (81.6%) were seizure free after complete resection, compared with 23 out of 94 patients (24.5%) whose resection was incomplete. The difference was statistically significant ($P < 0.001$). Temporal lobe location was more favourable than extratemporal location. Of 82 patients (68.3%) who underwent temporal resection within the temporal lobe, 56 were seizure free, in contrast to 102 out of 204 patients (50.0%) whose resection was extratemporal. The difference was relatively small but statistically significant ($P = 0.019$). The use of either invasive monitoring or intraoperative EcoG did not affect the surgical results.

The most visible and easily classified lesion was the balloon cell. As a result, a large number of the studies focused on whether the presence of balloon cells predicts surgical outcome. Conflicting results were found in these surgical series. Although some found that the presence of balloon cells was correlated with better outcome [106,107,119], others found the opposite relation [110], or no relation at all [105,115]. As a whole, data from a pool of 210 patients indicate that the presence of balloon cells is not a reliable prognosticator of seizure-free surgical outcome.

Conclusion

Intractable epilepsy is frequently associated with MCD; however, it is amenable to surgical treatment. Surgical outcome with this pathology relies on a precise identification of an epileptogenic zone and its complete resection. This task is complicated by the frequent occurrence of MCD in eloquent areas and the persistence of essential cortical function within the epileptogenic zone in some types of MCD. Despite the challenging nature of this pathology, surgical outcome has steadily improved owing to important insights into this group of pathologies brought on by genetics, imaging, electrophysiology and refinements in surgical techniques.

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73 Hemispherectomy for Epilepsy

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Introduction

When congenital or acquired unilateral extensive brain pathology is associated with medically intractable hemispheric epilepsy, the only successful treatment in terms of seizure control will be a complete removal of this hemisphere or a functionally complete disconnection of all its afferent and efferent fibres (hemispherectomy or hemispherotomy; in this chapter, both terms will be synonymously referred to as HS if not otherwise specified).

Following the pioneering work of Walter Dandy [1], who performed the first documented hemispherectomies in man between 1923 and 1928 in five patients with infiltrating gliomas of the right cerebral hemisphere, and the concomitant theoretical work of the French neurologist Jean Lhermitte [2], the Canadian Neurosurgeon Kenneth McKenzie was the first to perform (in 1936) an anatomically complete right-sided hemispherectomy for disabling epilepsy in a 16-year-old girl with infantile hemiplegia following head trauma. The procedure was successful and the patient remained seizure free from then on [3]. However, relatively little notice was taken of his report and the procedure became popular only after the published work of R.A. Krynauw in 1950 on a series of 12 young patients with infantile hemiplegia who underwent hemispherectomy for drug-resistant epilepsy, with successful seizure control achieved in 10 of them [4].

Since then, anatomical hemispherectomies have been performed worldwide, with extensive discussions and several proposals as to whether, and to what degree, the basal ganglia should be included in the brain volume to be resected. Over the subsequent 10 years, more than 260 such procedures for epilepsy patients with infantile hemiplegia were performed worldwide [5]. Following the first reports of superficial cerebral haemosiderosis (SCH) as a late and potentially lethal complication of anatomical hemispherectomy, due to chronic repetitive bleeding into the huge subdural cavity and into the remaining ventricles [6–8], several essential modifications have been proposed in the last 40 years, such as the hemidecortication procedure [9], the Oxford modification, which consisted of obliterating the subdural cavity and excluding this space from the ventricular system [10], or Rasmussen's functional hemispherectomy [11]. More recently, different surgical techniques with a minimum amount of cerebral tissue resection but functionally complete disconnection of the affected cerebral hemisphere have been developed. In 1992, Delalande [12–14] proposed the vertical parasagittal approach in order to disconnect the hemisphere in a vertical plane from within the lateral ventricle and coined the term 'hemispherotomy'. Other disconnection techniques were developed [15,16], such as Villemure's peri-insular hemispherotomy. This technique is derived from the classical concept of functional hemispherectomy, using a lateral approach above and below the insular cortex and through the lateral ventricle in order to proceed to the hemispheric disconnection [15]. The transsylvian keyhole functional hemispherectomy is a similar technique which allows the temporomesial resection and hemispheric disconnection through a transsylvian approach to the lateral ventricle across the circular sulcus of the insula [17]. At present, all of the above-mentioned techniques are applied by epilepsy surgeons around the world with apparently similar results on seizure control, although depending on the underlying pathology; however, there is variation with regard to perioperative risk and hospital course. Until now, very few publications have been able to address this issue of comparing different existing techniques [18,19].

Indications

Congenital or acquired unilateral brain lesions of different pathologies are capable of triggering severe, intractable epilepsy, originating from the entire or from major parts of the damaged hemisphere. The underlying aetiologies are infantile hemiplegia seizure syndrome, which includes pre- and postnatal injuries and vascular accidents that have formed large porencephalic cysts and which, historically, was the first hemispheric seizure disorder to be treated by hemispherectomy; Sturge–Weber syndrome, a phacomatosis associated with a more or less extensive unilateral leptomeningeal angiomatosis; the group of extensive malformations of cortical development with unilateral manifestation, including hemimegalencephaly; and Rasmussen's syndrome, a chronic unilateral encephalitis, which is unique among the seizure disorders considered for hemispheric surgery in that the first clinical manifestations, i.e. generalized or partial seizures followed by a progressive hemiparesis and hemispheric atrophy, will appear after an initial period of normal childhood development, with a median age of onset of about 5 years (14 months to 14 years) [20].

The time of prenatal injury with regard to brain development will determine if migrational and maturational disorders of cortical development will occur in addition: when injury happens before the 26th week of gestation, dysplastic grey matter adjacent to the porencephalic cavity and overlying polymicrogyria can be associated [21].

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A distinct pathology which can develop into a seizure disorder of hemispheric origin is the hemiconvulsion hemiplegia epilepsy (HHE) syndrome. Systematically described by Gastaut in 1957 [22], the HHE syndrome usually follows one or several initial prolonged febrile hemiconvulsions, with or without deficit, in early childhood and evolves, after a free interval of variable duration, into an intractable epilepsy, probably due to ischaemic damage from prolonged seizure activity. The epilepsy may be of focal origin, usually of the temporal lobe, but it may have a larger extension, with diffuse cortical and subcortical atrophy of the affected hemisphere.

Other pathologies that are less frequently encountered in the presurgical evaluation setting for HS are due to sequelae of cerebral inflammatory processes of bacterial or viral origin.

Patients who are considered for hemispheric epilepsy surgery have several clinical characteristics in common: they initially present or will progress with a contralateral hemiparesis, which is usually predominant in the upper limb and is associated with a hemisensory deficit which is difficult to assess. Most children will present with a fixed or progressive homonymous hemianopsia, dependent on the underlying pathology, but the extent is difficult to assess in younger children. When the dominant cerebral hemisphere is affected, language development may be impaired to a certain degree or, as in Rasmussen's encephalitis, will eventually deteriorate in a progressive manner. The frequent contralateral seizure spread will interfere with early childhood development, with a deleterious effect on cognitive and behavioural functions over time. This may lead to severe epileptic encephalopathy, particularly in pathologies with very early seizure onset, as is frequently the case in extensive malformations of cortical development.

Diagnostic evaluations

Clinical findings

When children with refractory hemispheric seizure disorders are being considered for hemispheric surgery, they already present with a contralateral neurological deficit (motor, sensory, visual) and, to a variable degree, impairment of cognitive and language functions, particularly when the left hemisphere is affected. Severe cognitive impairment may also indicate continuous subclinical epileptic discharges, as in continuous spike waves during slow-wave sleep, clinically manifesting in significant language and behaviour disturbances [23,24] or involvement of the opposite 'healthy' hemisphere in the disease process.

On the other hand, children who eventually develop Rasmussen's syndrome will have had a normal development before the seizure onset and, from the time the chronic encephalitis is suspected, neurological and subsequently higher cortical function decline will parallel the progressively disabling seizures. The decision of when to propose hemispheric surgery in these patients will therefore depend on the actual degree of the deficits and severity of epilepsy, particularly in left hemispheric pathology.

Motor function

Preoperatively, all children will present with a certain degree of contralateral motor impairment (muscle strength, range of motion, muscle tone). After HS, muscle strength in the proximal upper limb and in the lower limb will eventually return to the preoperative level, whether in the distal arm and hand, muscle tone is increased and strength remains decreased compared with the preoperative level, with permanent loss of finger dexterity [25,26]. This phenomenon might be explained by the fact that hand movements are more under the control of the corticospinal pathways, whereas the locomotor task of the lower limbs is more under the control of the spinal neuronal circuits [27]. Furthermore, subcortical regions, such as the cerebellum and the mesencephalic locomotor region of the brainstem or ipsilateral corticospinal pathways, might contribute to the ability to ambulate following HS [28]. In general, patients who are ambulatory prior to HS remain so thereafter, independent of the underlying pathology [18]. In a retrospective study including 111 patients undergoing hemidecortication, 89% were able to walk without assistance after surgery [29]. Those who where unable to walk had prior immobility due to the underlying process, major postoperative complications or persisting seizures. On the other hand, it has been shown that children with a better cognitive development before surgery had more improvement in global motor function after hemispherectomy than children with a lower cognitive level [25].

Visual pathways

Contralateral homonymous hemianopsia will either remain unaltered if already present before surgery or will result following HS [25]. Recently, the capacity to process visual information in the blind visual field (blindsight) has been demonstrated in hemianopic patients following hemispherectomy by means of functional MRI (fMRI) and diffusion tensor imaging tractography [30–32]. The possible capability of the retinocollicular pathway, which does not degenerate completely as a result of cortical hemispherectomy in the same hemisphere, in processing visual inputs (projecting to the contralateral cortex) has been hypothesized in this phenomenon [30,31,33].

Language

When left or dominant hemispheric disconnection is carried out before the age of about 5 years (a period considered critical for language lateralization) postoperative language outcome is in general excellent. Thus, homologous language zones in the right (minor) hemisphere are capable of taking over receptive as well as expressive language functions. In contrast, in acquired pathologies (such as Rasmussen's syndrome) with a later seizure onset following an initial period of normal development preoperative language skills will be impaired in most cases and postoperative recovery may well improve but never return to normal. Hertz-Pannier *et al.* [34] described a 9-year-old boy who underwent left hemispherotomy for epilepsy with Rasmussen's encephalitis, with disease onset at age 5.5 years after normal language acquisition [34]. At 1.5 years post surgery, language function had considerably improved and fMRI during word generation demonstrated activation in the right inferior frontal, temporal and parietal regions, homologous to the preoperative left-sided fMRI activation pattern. On the other hand, Voets *et al.* [35] described a pre- and postoperative language fMRI study of a similar case of a boy with Rasmussen's encephalitis who underwent left

hemispherectomy at the age of 14. The postoperative fMRI revealed right inferior frontal as well as anterior insular activation, whereas the preoperative study had shown engagement of a bilateral frontotemporal network for the same language task. More recently, in a fMRI study involving six patients undergoing hemispherectomy (three left and three right), the patients showed a variable pattern of language activation in the inferior frontal region (Broca's area and its right homologue) along with consistent and typical activation in the temporal and precentral regions [36]. The extent of the activated right inferior frontal region seems to determine language outcome in children after left hemispherectomy.

In general, recovery of expressive language functions lags behind recovery of receptive functions. This was confirmed in a study by Boatman *et al*. [37] on six children aged 7–14 years with Rasmussen's encephalitis undergoing left hemispheric decorticectomy [37]. By 1 year after surgery, receptive functions were similar to, or surpassed, the presurgical performance, whereas expressive functions, such as naming and spontaneous speech, were still impaired. These authors did not find other factors to influence language outcome, such as the time interval from seizure onset to surgery or the patient's presurgical IQ.

In our retrospective study [14], including 83 patients with different underlying aetiologies who underwent hemispherotomy, language function was evaluated in 58 French native speakers with the Vineland Adaptive Behavior Scale [38]. In general, children showed a better communication score after right hemispherotomy than after left hemispherotomy, independent of the underlying pathology, and children in the Rasmussen group performed best in all the four skill domains. The time interval from onset of seizures to surgery was inversely correlated with the Vineland scores in three out of the four domains – socialization, daily living skills and communication – in right as well as in left hemispherotomy patients and for all aetiology groups [14].

Special considerations in Rasmussen's encephalitis

Children with Rasmussen's encephalitis who are considered for HS are in a different clinical situation from those with refractory epilepsy from other aetiology groups, and controversy exists as to whether HS should be performed early in the disease course or if it should be delayed in order to await spontanous progressive impairment, similar to what would be inflicted by early surgery. Neurocognitive development is normal before seizure onset and the functional pattern of deterioration will follow partial seizure activity. At the time of the first presentation for presurgical evaluation, motor hemideficit will be at most mild and, particularly, the hand function preserved. Successive motor deterioration will depend on the intensity of seizure activity and progressive focal cortical atrophy. Language and intellectual capacities are initially unimpaired, even in left hemisphere involvement, but will later on decline to a certain degree, although not always with a predictable time course. Steroid therapy can lead to a transitory remission, thereby further delaying the decision to operate.

Therefore, decline and eventual reorganization of cortical functions within the contralateral hemisphere will show an evolutionary but variable course, depending on factors such as age at seizure onset, the intensity and frequency of seizures, and the child's age at surgery.

After HS, children with Rasmussen's encephalitis show the most pronounced postoperative motor deficits compared with all other aetiologies [14], particularly concerning distal arm and hand function, which will necessitate an intensive and long-lasting rehabilitation programme.

HS of the left hemisphere might further worsen pre-existing language impairment, especially for expressive capacities. The degree of deficit and its long-term recovery will depend on the age at surgery, but the variability in hemispheric language shift and the participation of the healthy contralateral hemisphere in the language network before surgery are probably due to other factors as well.

Pulsifer *et al.* [39], in a pre- and postoperative cognitive study including 71 children who underwent hemispherectomy for different aetiologies, found a significantly lower general IQ score as well as receptive and expressive language performance scores in children with left hemispheric Rasmussen's syndrome than in those with right hemispheric, whereas they did not confirm such a side difference for cognitive outcome in children operated for cortical dysplasia or vascular aetiologies.

In our own patient cohort, as mentioned below, children with Rasmussen's encephalitis and left hemispherotomy fared better in language performance when surgery was performed at a younger age and when there was a shorter delay between onset of epilepsy and time of surgery. These results are in favour of an early decision towards surgery, as interhemispheric language shift caused by the disease process itself is obviously not a sufficient precondition for a good postoperative language outcome. On the contrary, our observation rather corroborates the hypothesis of a reinforced new language network after early HS.

Evolution of the surgical techniques

Since anatomical hemispherectomy for intractable epilepsy was applied for the first time in 1938, several fundamental modifications have been proposed, The classical procedure of anatomical hemispherectomy [1,4] was progressively abandoned in order to avoid early and late complications, such as intraoperative blood loss [19,40] or the incidence of fatal brainstem shift towards the resected side [41]. This process was accelerated from the late 1960s onwards, when the first reports of SCH as a severe late complication in as many as one-third of the patients undergoing hemispherectomy were published [8,42].

Functional hemispherectomy

In 1983 Theodore Rasmussen [11] published his experience of eight patients in what he called a 'functionally complete but anatomically subtotal procedure' – the *functional hemispherectomy*. This novel technique evolved from his observation that none of the patients who had previously been operated with a subtotal hemispherectomy suffered SCH in the long term, implying that the retention of a substantial cerebral volume on the operated side would reduce the size of the subdural cavity and could thus prevent brainstem shift and repetitive subdural bleeding with SCH formation. The success rate in controlling seizures, however, was disappointing and he therefore sought to develop an

anatomically subtotal but functionally total hemispherectomy. Functional hemispherectomy is based on a combination of a temporal lobectomy, including removal of the mesial structures, and extensive excision of the central region, while performing a complete subpial disconnection of the frontal, posterior parietal and occipital lobes, which are left in place together with their blood supply (Fig. 73.1). Epileptogenic insular cortex may additionally be resected. Indeed, in a published series of 34 patients who underwent functional hemispherectomy, none developed SCH after a median follow-up of 8 years [43].

The *modified hemispherectomy* originated at Oxford and was popularized by Adams [10,44]. In order to prevent the formation of chronic subdural haematoma membranes, this modification consisted in creating a wide dural detachment which is then sutured down to the falx tentorium and the dura of the skull base, thus turning the large subdural into an epidural space. Adams added to this technique the separation of the remaining subdural cavity from the ventricular system by obstructing the foramen of Monro with a plug of muscle, in order to avoid the chronic exposure of the ventricular system to blood products and subsequent hydrocephalus formation.

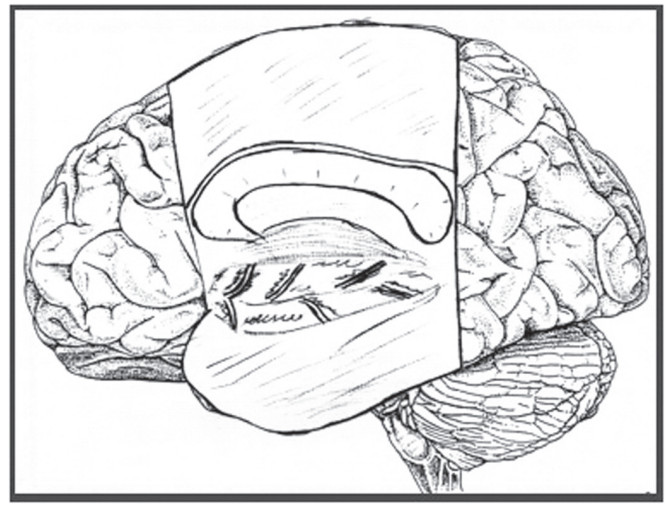
Hemidecortication was proposed by Ignelzi and Bucy in 1968 [9,45–47] and consisted in a hemispheric excision of the grey matter only, thereby sparing as much as possible of the white matter and avoiding opening of the lateral ventricle. This suggestion was based on the idea that removal of the entire epileptogenic cortex would be sufficient to stop seizure activity. Particularly in the case of Sturge–Weber syndrome, the cortical removal would include all areas with pial angiomatosis, but could spare cortical regions not affected, as is frequently seen in temporomesial cortex. The effectiveness of this technique in seizure control, however, was diminished in children with diffuse cortical dysplasia and hemimegalencephaly, as deeper-seated epileptogenic tissue can be at the origin of persisting seizures.

In order to further decrease complication rates due to the volume of brain tissue removal, intraoperative blood loss and duration of surgery, less invasive techniques have been developed, further increasing the ratio of disconnection to resection and requiring a smaller skin incision and bone flap.

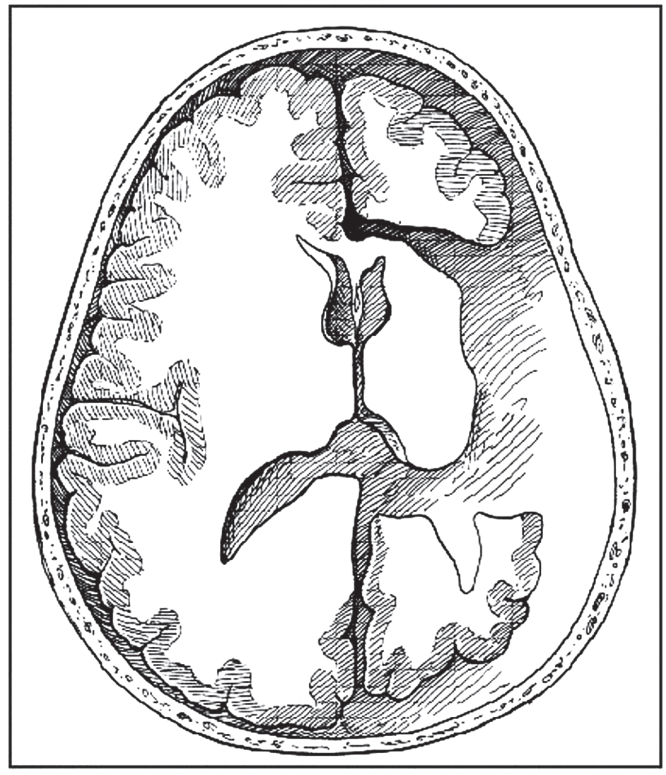
This concept turned out to replace the term hemispherectomy with that of *hemispherotomy*, proposed for the first time by Delalande in 1992 [12,13,48]. He described a vertical approach by opening the roof of the lateral ventricle below the frontocentral region and performing a vertically oriented hemispheric disconnection from within the ventricle. This technique is described in more detail below. The authors' experience with this *vertical parasagittal hemispherotomy* amounts to 200 such procedures to date. The technique and its results have been recently published for a part of this population [14].

Other hemispherotomy techniques have since been proposed, through a lateral peri-insular or transsylvian approach.

The *peri-insular hemispherotomy* described by Villemure and Mascott [15], which is derived from the concept of functional hemispherectomy, uses a small lateral supra- and infrainsular window through the frontoparietal and temporal opercula in order to reach the lateral ventricle. From here, resection of the amygdala and anterior hippocampus, as well as callosotomy and complete hemispheric disconnection, are performed. The insular cortex may additionally be excised.



(a)



(b)

Fig. 73.1 Drawings of a functional hemispherectomy as developed by Th. Rasmussen: lateral (a) and axial (b) plane, demonstrating resection of the temporal lobe, the central region and the insular cortex, with disconnection of the remaining frontal and parieto-occipital lobes. Both images reproduced with permission from Villemure JG. Cerebral hemispherectomy for epilepsy. In: *Operative Neurosurgical Techniques*, 3rd edn. Schmidek HH, Sweet WH (eds). Philadelphia: WB Saunders, 1995.

A generally similar technique, the transsylvian transventricular functional hemispherectomy, was proposed by Schramm *et al.* [17]. After resection of the anterior temporomesial structures and transsylvian exposition of the insular cortex, the lateral ventricle

is accessed through the circular sulcus of the insula and a callosotomy and hemispheric disconnection can be then carried out.

Shimizu and Maehara [49] have described another modification of the peri-insular hemispherotomy, beginning with a resection of the frontoparietal operculum and performing the different steps of complete hemispheric disconnection through this opercular resection cavity.

The lateral disconnection techniques are more difficult to perform in pathologies with minimal cerebral atrophy or even hypertrophic forms of cortical malformations, such as in hemimegalencephaly. In this pathology, the situation can be further complicated by a distorted anatomy of the lateral ventricle, the callosal body and other midline structures. The authors of the lateral approaches therefore recommend adapting the technique in these cases by enlarging the volume of excision, which also provides more space for postoperative brain swelling, which can particularly occur in hemimegalencephaly.

Vertical parasagittal hemispherotomy

At our institution, hemispheric surgery for epilepsy has been performed with one single technique, the vertical parasagittal hemispherotomy, which was first described by Delalande in 1992. To date, our personal experience with this technique amounts to 200 hemispherotomies over a period of 18 years. The distribution of the different underlying pathologies in our population is listed in Table 73.1. We recently reported the surgical technique in detail, as well as the postoperative results for a part of our patient population [14].

The technique can be described as follows. Through a small parasagittal frontoparietal craniotomy, a limited cortical resection of approximately 3 cm × 2 cm is performed and pursued, until the central part of the lateral ventricle is unroofed and its anatomical landmarks exposed (see Plate 73.1a). The corpus callosum is identified by following the roof of the lateral ventricle mesially. As for the whole hemispheric disconnection, the ultrasonic aspirator is used at a low level of vibration. The first step of the hemispherotomy will be a posterior callosotomy through this parasagittal approach. Resecting the splenium to the midline will expose the roof of the third ventricle and the arachnoid over the ambient cistern. From here, the dissection is pursued laterally to the choroidal fissure behind the pulvinar, thereby disconnecting the posterior column of the fornix at the level of the ventricular trigone (see Plate 73.1b). A strictly vertical incision lateral to the thalamus is then performed from this point anteriorly, by opening the roof of the temporal horn up to its most anterior part. This step will interrupt all fibres from the insular cortex as well.

Next, the callosotomy will be completed anteriorly. As for its posterior part, the ultrasonic dissection is performed intracallosally up to the interhemispheric cistern, with the exposed pericallosal arteries serving as a guide. This is followed by a limited resection of the most posterior part of the gyrus rectus. This resection allows one to visualize, across the arachnoid, the first segment of the anterior cerebral artery and the optic nerve, and provides space for the following straight incision oriented laterally through the caudate nucleus, in order to finally join the dissection line at the anterior point of the lateral incision. This last dissection will cut all the connections from the anterior temporal lobe, the amygdala and the frontal lobe. The hemispherotomy is now complete, having isolated the entire epileptic cortex from the subcortical structures.

The surgeon's vertical perspective allows a relatively clear identification of the anatomical key landmarks adjacent to the ventricle and facilitates the hemispheric dissection around these core structures, even in anatomically difficult pathologies, such as extreme forms of hemimegalencephaly or extensive post-ischaemic/-traumatic sequelae.

Furthermore, the vertical hemispherotomy allows us to perform, from within the ventricle, the whole tissue dissection subpially, thus avoiding manipulation of important vascular structures, such as the perforating branches from the anterior and middle cerebral artery or the densely packed insular branches.

On postoperative axial and coronal MRI, the line of the hemispheric disconnection can be easily identified (see Plate 73.1c).

Table 73.1 The different pathologies underlying unilateral hemispheric epilepsy.

Number of patients operated on by vertical parasagittal hemispherotomy for each category at our institution (total number of hemispherotomies from April 1990 to April 2008, n = 200) (right hemisphere 89, left hemisphere:111)

Malformations of cortical development
n = 87 (hemimegalencephaly: 40) (43.5%)

Rasmussen's encephalitis
n = 46 (23%)

Infantile hemiplegia (including perinatal stroke, brain haemorrhage, post-traumatic and post-infectious sequelae, miscellaneous)
n = 43 (21.5%)

Sturge–Weber syndrome
n = 24 (12%)

Seizure outcome

Once an appropriate patient selection for HS has been conducted, the postoperative outcome in terms of seizure control will be among the best in epilepsy surgery. In 90–95% of the patients, surgery leads to a worthwhile improvement from seizure reduction, and between 65% and 80% of the patients (all pathologies included) will be seizure free [14,18,19,29,50]. Devlin *et al*. [25] reported a somewhat lower rate of seizure-free children in their hemispherectomy series (52%). However, children with migrational disorders and hemimegalencephaly, who have the lowest seizure-free rates in all published series, were predominant in their reported population.

In all series to date, patients with migrational disorders, in particular with hemimegalencephaly, had a lower chance of being seizure free following HS (51–63%) than all other aetiologies [14,18,29,50].

Long-term outcome (>5 years) has been reported to be less effective with an overall decrease in seizure freedom from 76% at 1 year postoperatively to 58% at 5 years' follow-up [50]. Long-term follow-up in our own population (mean: 4.4 years) does not support this finding, with no decrease in seizure-free rates during the entire observation period [14].

Another important issue is whether the type of HS technique has an influence on seizure outcome. This has been adressed by

only a few authors, as most epilepsy surgeons who perform hemispheric surgery use only one single technique, and all but one published reports to date are from single centres. Cook *et al.* [19] compared three different hemispherectomy techniques (anatomical hemispherectomy, Rasmussen's functional hemispherectomy and a modified lateral hemispherotomy technique), applied in 115 patients over a 16-year period at a single centre by three neurosurgeons. They found perioperative risk and hospital course varied significantly depending on the techniques as well as the underlying pathology; there were significantly fewer perioperative problems related to blood loss, shorter times spent in the intensive care unit and shorter total hospital stays in patients undergoing hemispherotomy [19]. Differences in seizure control were not significant when comparing the three techniques, although there was a trend towards better outcome for all pathologies following hemispherotomy.

Holthausen *et al.* [18] conducted the largest retrospective and the only multicentric study to date, including 333 patients who were operated by one out of five different hemispherectomy or hemispherotomy techniques in 13 participating centres. Overall, 70.4% became seizure free, with a minimum follow-up of 6 months.

Regarding the different techniques, the best results were achieved with hemispherotomy and with Adam's modification (81.9% patients seizure free) compared with anatomical hemispherectomy, functional hemispherectomy and hemidecortication (64.1% patients seizure free). However, this difference did not reach statistical significance. In none of the pathology subgroups did the patient's age at surgery and the duration of the epilepsy correlate with a less favourable outcome.

The lowest seizure-free score was achieved in patients with malformations of cortical development (56.6%) and the best score in patients with Sturge–Weber syndrome (82.1% seizure free), followed by hemiatrophy (77.3%), Rasmussen's encephalitis (77.1%), vascular insults (76.1%) and 'others' (67.9%).

In our own published series, 74% of patients were seizure free following vertical parasagittal hemispherotomy, with no seizure recurrence after long-term follow-up and there was no necessity to reoperate children [14].

Postoperative seizures

Overall, approximately 5–10% of the patients undergoing HS will eventually not benefit from this surgery in terms of seizure control, with even higher failure rates being reported in children with migrational disorders, in particular those with hemimegalencephaly.

Theoretically, persistent or recurrent seizures might be explained by one of the following mechanisms:

- The epileptogenic tissue within the affected hemisphere has not been completely removed or disconnected.
- The epileptogenic tissue includes deeper subcortical structures, such as the basal ganglia, that were not included in the tissue volume to be resected or disconnected.
- Independent seizures arise from the contralateral hemisphere which was judged 'normal' in the presurgical evaluation.

The first point relates to the surgeon's experience and familiarity with the applied surgical technique. In our own patient population, we have performed 'second-look' surgery in two children with persisting seizures, after postoperative high-resolution MRI indicated a possible incomplete disconnection, and this proved to be the case in one child.

The second point is rather hypothetical but may be the reason for surgical failure in patients with cortical migration disorders, with a higher probability of finding dysplastic tissue within the subcortical structures. This is particularly the case in children with hemimegalencephaly.

The third point can never be completely excluded but emphasizes the requirement of a thorough presurgical evaluation of the contralateral hemisphere as well, by means of EEG analysis, structural and – if possible – functional imaging. In this respect, Rintahaka *et al.* [51] found a higher incidence of contralateral hypometabolism on FDG-PET studies in children with hemimegalencephaly and surgical failure following hemispherectomy, indicating structural abnormalities at the microscopic level [51]. On the other hand, Soufflet *et al.* [52], in a study including 13 patients with hemimegalencephaly who were evaluated with prolonged EEG recording and ^{133}Xe-SPECT measuring cereberal blood flow (CBF) pre- and postoperatively, found pathologically elevated CBF values in the hemisphere contralateral to the hemimegalencephaly [52]. This finding correlated with diffuse interictal spike activity and normalized soon after hemispherotomy, indicating that normal CBF function contralateral to the pathology can be restored. In hemimegalencephaly, some bilateral neuropathological changes have been proved following autopsy [53,54].

Early and late complications

Intraoperative complications in HS will determine the intraoperative and early postoperative morbidity and are mainly due to excessive blood loss, as may be particularly the case in children with hemimegalencephaly, a disorder associated with very early and severe seizure onset. Together with the group of extensive unilateral cortical dysplasias, these are the youngest patients to be operated on, frequently in early infancy. Significantly higher blood loss, which can reach an entire blood volume or more, and longer duration of surgery in children with hemimegalencephaly compared with all other aetiology groups (from authors' personal experience: see also ref. 50) have been related to young age, a more difficult anatomical situation with extensive cortical and subcortical hypertrophy, an anatomically distorted ipsilateral ventricle and corpus callosum, an increased blood flow to the megalencephalic hemisphere and a presumably abnormal venous drainage, which has been described in several cases with excessive bleeding [40,55,56]. Abnormal venous drainage can in turn be the reason for considerable postoperative brain swelling. In young infants in particular, possible problems from hypothermia, volume derangement, electrolyte imbalances and coagulative impairment during long surgery, and blood loss have to be taken into account.

Besides the specific anatomical features of each hemispherectomy/-otomy technique, operative blood loss seems to be a critical distinguishing parameter. The only comparative study addressing this issue to date has demonstrated a significantly reduced intraoperative blood loss and associated parameters, as well as a reduced postoperative intensive care stay in children operated by hemispherotomy as compared to anatomical or functional

hemispherectomy for all aetiology groups, including hemimegalencephaly [19]. These authors demonstrated that modified lateral hemispherotomy had the significantly lowest overall complication rate (11% vs. 35% and 34% for anatomical and functional hemispherectomy, respectively) and a reduced necessity of postoperative shunting (22% vs. 78% for anatomical hemispherectomy), although the shunt rate was even lower following functional hemispherectomy (9.4%).

Among the surgery-related morbidities, the development of internal and/or external hydrocephalus is relatively frequent, occurring several days to several months after HS but rarely as a late complication beyond the first postoperative year, and which will necessitate the placement of a ventriculoperitoneal or subduroperitoneal shunt. The incidence of postoperative hydrocephalus varies from 5% to 39% as reported in several recent series using different techniques of hemispherotomy [19,14,25,29,50,57]. Note that some authors do not consider hydrocephalus to be a postoperative complication [50]. The incidence seems to be elevated in children with hemimegalencephaly [14,25,57], although other authors have not found significant differences among the different pathologies [50].

Unexplained high fever early in the postoperative course, probably related to aseptic meningeal reaction, is a common observation and has been described by several groups [25,58].

In general, postoperative wound infections and haemorrhages seem to have the same low incidence as with other neurosurgical procedures of similar extent and duration and will deserve the same prophylactic and therapeutic measures.

The above-mentioned SCH as a severe late complication after anatomical hemispherectomy has led to newer, less invasive techniques with virtually no cases reported in the more recent larger series with sufficiently long follow-up. Nevertheless, some authors report the absence of SCH in more recent anatomical hemispherectomy series, relating this improvement to a meticulous haemostasis [19,59].

Conclusion

When unilateral hemispheric refractory epilepsy has been well documented, including a meticulous analysis of the integrity of the contralateral hemisphere by means of structural and functional imaging, ictal EEG and clinical seizure semiology, in order to rule out bilateral pathology, HS is a very effective surgical procedure, with a rate of seizure control that approaches the success rates in surgery for mesial temporal lobe epilepsy. Seizure outcome will depend primarily on the underlying pathology and is inferior in patients with extensive malformations of cortical development, including hemimegalencephaly. Intellectual and behavioural development will, in addition, be influenced by the age at seizure onset and the age at surgery, with a better chance for higher cortical function recovery when HS has been performed in earlier childhood.

Hemispherotomy is the logical continuation of the functional hemispherectomy, by further reducing the amount of excision in favour of disconnection, with the same indications and the same effect on seizure control. In our own experience with the vertical parasagittal hemispherotomy, as well as that of other neurosurgeons with the lateral approach hemispherotomy, overall surgery-related morbidity and hospital stay are significantly reduced, due to a very limited amount of cerebral tissue removal, a shorter length of the surgical procedure and a reduced amount of blood loss. Moreover, the incidence of shunt-dependent hydrocephalus seems to be improved by the disconnective techniques or other functional hemispherectomy techniques compared with anatomical hemispherectomy.

Once the hemispheric resection or disconnection is supposed to be complete, a failure to control seizures is most probably due to epileptogenic tissue within the remaining opposite hemisphere. On the other hand, when abnormal interictal and ictal EEG activity is recorded over both hemispheres during the preoperative assessment it should not necessarily preclude the therapeutic option of hemispheric surgery, as it may be due to rapid discharge propagation from the epileptogenic hemisphere.

The timing of surgery depends primarily on factors such as duration and severity of the seizure disorder, dynamic evolution of the disease, and actual neurological and cognitive state. Particularly in children with malformations of cortical development and with Rasmussen's encephalitis of the language-dominant hemisphere the decision when to operate remains a challenge, in order to achieve the best possible long-term cognitive development, degree of autonomy and quality of life.

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74 Corpus Callosotomy

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Introduction

Surgical section of the corpus callosum has attracted enormous attention since its earliest reports, in large part the result of fascination with its neuropsychological consequences and implications. It was first performed nearly 70 years ago by Van Wagenen and Herren [1], who had observed that patients sustaining stroke or tumour progression destroying the corpus callosum often had improvement in an associated seizure disorder. There was laboratory evidence supporting the rationale for this procedure, notably that of Erickson [2], who in non-human primates demonstrated prevention of the spread of the epileptic discharge to the opposite hemisphere when the corpus callosum had been divided [2]. Following this early work, a small number of clinical series were reported [3–25], but it was not until the late 1980s that the procedure was widely adopted as a surgical option in medically intractable epilepsy patients who were not candidates for resective procedures. Today, most epilepsy centres perform commissurotomy and it retains an important role in the armamentarium of interventions for intractable epilepsy.

Indications

Resection of an epileptogenic region with the goal of surgical cure has always been the surgical procedure of choice, but in those patients with generalized seizures in whom a discrete epileptogenic region cannot be identified or resected, surgical disruption of secondary generalization is a reasonable option. Other palliative procedures, including multiple subpial transection, vagal nerve stimulation and deep brain stimulation, have also been developed and the strategy for optimal utilization or prioritization of these various non-ablative strategies remains to be determined.

From the earliest days of callosotomy it has been appreciated that drop attacks (variously classified as atonic and akinetic seizures) are among the most likely of seizure types to benefit from disconnection; tonic and tonic–clonic generalized seizures similarly have been shown to be significantly reduced [8–13,15–20,22–106]. Given the difficult evaluation in this patient population, it is both understandable and reasonable that many patients have undergone callosal section largely on the basis of their seizure semiology.

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The pathological substrate of the seizure disorder historically has played a secondary role in patient selection for this procedure. A spectrum of disease has been encompassed in clinical series. Williamson [92] looked at surgical outcomes in terms of clinical diagnoses and classified patients into groups of infantile hemiplegia, *forme fruste* infantile hemiplegia, Rasmussen's syndrome, Lennox–Gastaut syndrome, frontal lobe epilepsy and other secondarily generalized epileptics. Slightly better outcomes were found in the first two groups but there was sufficient improvement in all categories to justify surgical intervention.

Electroencephalography and video-electroencephalogram (EEG) monitoring have influenced patient selection principally in demonstrating the presence or absence of a resectable seizure focus. EEG findings in patients selected for callosotomy have been analysed by a number of investigators [50,107–113]. Correlating EEGs with surgical results, Geoffroy *et al*. [37], Spencer *et al*. [23] and Matsuzaka *et al*. [114] all reported better results in patients with lateralized EEG abnormalities. The majority of patients have evidence of bilaterally synchronous epileptiform activity and this does not necessarily represent a bad prognostic sign. The significance of bilateral, independent foci remains undetermined.

Demonstration on neuroimaging of lateralized structural lesions has been believed to be associated with a better surgical outcome [10,23], but in the selection process their presence or absence has always been secondary to clinical and electrophysiological information. The impact of neuroimaging on the callosotomy experience has been limited. As imaging technologies continue to evolve with increasing sensitivity and specificity, they are directing such aspects of the seizure evaluation as intracranial recording electrode placement, and this will obviously affect patient selection and perhaps the surgery itself.

Candidates for callosal section are patients who have medically intractable epilepsy in whom a resectable seizure focus cannot be identified and whose generalized seizures are believed likely to be ameliorated by disruption of seizure propagation. Patients in whom seizure semiology, electrophysiological studies, neuroimaging and neuropsychological testing have shown localized disease amenable to resection are excluded. The remaining candidate pool will be heterogeneous, including patients with infantile hemiplegia, *forme fruste* infantile hemiplegia, Rasmussen's syndrome, Lennox–Gastaut syndrome, frontal lobe epilepsy and other secondarily generalized epilepsies.

At our institution, selection criteria include (1) medical intractability of at least 2 years' duration (and typically longer), with exhaustive anticonvulsant regimens and documented adequate serum anticonvulsant levels; (2) generalized seizures, usually but

not necessarily major motor or atonic in type; (3) exclusion of a resectable seizure focus; and (4) potential functional benefit if improvement in the seizure disorder is achieved. We have not automatically excluded patients from surgery because of retardation, age, mixed hemisphere dominance [54,81], lack of demonstrable partial seizure onset or bilaterally independent EEG abnormalities, although it is recognized that the likelihood of success may be less in certain instances. Although the outcome of a seizure-free patient is always hoped for, this is achieved in only 5–10% of cases [115,116]. The goal of surgery with callosal section is distinguished from that of other epilepsy surgeries as it is usually palliative rather than curative.

Surgical technique

Early clinical series often included division of the corpus callosum, the underlying hippocampal commissure and additional structures, including the anterior commissure and, in some instances, one fornix [1,3,5–9,11]. Nearly all series today restrict division to the corpus callosum and, in posterior or complete callosal section, to the hippocampal commissure that is immediately apposed to the ventral aspect of the posterior portion of the callosum. There remains variation, however, with regard to which part or how much of the structure is divided. Seizure outcome appears to have some correlation with the extent of section [79,88]. As neuropsychological consequences of callosal section are encountered primarily with complete section [117,118], most centres today usually divide the anterior three-quarters and spare the splenium at initial surgery. Completion of the section can then be performed in those patients who fail to obtain an adequate response to such surgery. Exceptions to this approach are division of a smaller, select portion of the callosum, division of the posterior half as an initial procedure and division of the entire callosum in one operation. The presurgical evaluation and preoperative substrate may influence the consideration of these alternatives.

Diffuse or bilateral disease for which commissurotomy may be an appropriate strategy may be suggested by the history, neurological examination and cognitive evaluation, and these may contribute in the consideration of the risk–benefit ratio for partial or complete section. The sensory dissociation whereby visual, auditory or tactile information received by the non-dominant hemisphere may not be accessible to the speech-dominant hemisphere is of diminished consequence in the severely impaired individual, and in such a setting complete section may be a reasonable surgical approach. This is especially true if drop attacks, which usually respond to anterior section, are not the predominant seizure pattern. If presurgical evaluation, including electrophysiological studies, demonstrates predominantly parietal–occipital disease, it may be appropriate to consider posterior partial section as the first stage.

Consideration of the epileptogenic substrate may be important for reasons similar to those in the preoperative evaluation. A more discrete pathology may direct one towards an appropriate partial section [16], and diffuse disease may render any partial section futile. The correlation between extent of disease and successful section, however, is insufficient to place great reliance on these factors. Lateralized pathology does have a modest but worthwhile role in determining the side of the interhemispheric approach; this is usually on the non-dominant right side, but in the setting of an atrophic left hemisphere or right hemisphere language dominance, surgery from the left side of the falx may be indicated.

The patient is usually placed under general anaesthesia; intraoperative electroencephalographic recording, when performed, has been primarily for investigative purposes. Tailoring of the length of resection based on intraoperative EEG information has been advocated by at least one centre [55,56,119]. However, given the reality of often insufficient abnormal interictal EEG findings intraoperatively, as well as the observation that subsequent seizure propagation may occur across remaining, adjacent callosal fibres, most have not adopted this practice. The patient is placed in a supine position on the operating table, with the head unturned and secured in a three-point pin fixation. For the anterior division, the neck is kept in neutral position; for the posterior division, flexion of approximately 20° facilitates exposure. Alternatively, one may position the head parallel to the floor such that the hemisphere to be retracted is dependent, thereby allowing gravity to help provide the exposure [35,53]. This has the appeal of minimizing any retracting force placed interhemispherically, although whether this retraction is significant enough to warrant the perhaps less comfortable and differently oriented horizontal positioning is open to discussion.

The incision and type of craniotomy used is a matter of the surgeon's personal preference. We have used linear incisions and 5-cm trephinations [11,120], but the actual type and extent of craniotomy is relatively unimportant. A 9-cm transverse incision with one-third of its length across the midline and placed 2 cm in front of the coronal suture is used for the anterior procedure. A similar incision and trephination at the level of the parietal eminence is employed for the posterior procedure. The placement of the craniotomy across the sagittal sinus requires caution but facilitates exposure down the interhemispheric fissure with minimal retraction, and this is important.

Determination of the location of parasagittal draining veins prior to transcallosal procedures has been advocated, but this has not been a routine step for most centres, including ours. It has always been possible to work on either or both sides of such a vein without requiring its sacrifice using a microsurgical technique. Nevertheless, Apuzzo's observation [121] that in 42 out of 100 angiographic studies significant veins were noted to enter the sagittal sinus within 2 cm of the coronal suture, with 70% of these posterior to the suture, is of interest. Such angiographic information may be available in those patients who have previously undergone amytal testing or in whom MRA techniques have delineated parasagittal venous structures.

The dura is opened in the conventional manner, with a curvilinear incision and reflection on the sagittal sinus. Dissection begins down the interhemispheric fissure under loupe magnification, and retraction is aided by the earlier administration of mannitol (1 g/kg). Pressed Gelfoam (Upjohn, Kalamazoo, MI, USA) is used to protect the exposed cortex, and a Greenberg self-retaining retractor is placed before use of the operating microscope. Gentle retraction is accomplished with a single retractor blade on the ipsilateral hemisphere and, very occasionally, an additional blade retracts the inferior aspect of the falx or contralateral cingulate gyrus.

Adhesions between the hemispheres may make initial exposure difficult, especially when there is a history of previous infection or trauma. With patient microsurgical technique, one can generally obtain good exposure; approaching the callosum more posteriorly and utilizing the deeper extension of the falx can prove helpful in this situation. The corpus callosum is distinguished from the more superficial cingulate gyrus by its glistening white appearance, and exposure along the length of callosum to be divided is obtained prior to entering the commissure. The pericallosal arteries are identified overlying the callosum and care is taken to avoid their injury. Actual sectioning of callosal fibres is usually carried out between these arteries, although division lateral to these vessels can be performed if more convenient.

It is standard practice today to use the operating microscope, whose superior magnification and illumination have proven invaluable during the exposure and actual sectioning. Bipolar cautery is used for coagulation of small vessels supplying only the callosum itself. The actual division of callosal fibres is carried out with a microseptal or microsuction tip. The ultrasonic aspirator may prove to be of greater utility in this step as it becomes more refined and thinner.

The slightly darker, bluish appearance of the underlying ventricular ependymal surface, described in early reports of callosal section recommending its use as the limit of division [11], will indicate the approach to the ventral aspect of the callosum. The alternative of identifying the midline, however, offers numerous advantages increasingly evident over the course of our series. These include unequivocal assurance of completeness of fibre division, elimination of possible lateral deviation (especially in the frontal region), decreased likelihood of entering the lateral ventricle, and less operative time. A blunt microinstrument is gently swept from side to side as the callosum is nearly traversed, and this will usually expose the midline cleft between lateral ventricles. This is usually easiest at the most posterior portion of the genu or the anterior portion of the body. Once this cleft has been identified, the remainder of the section is easily accomplished.

The actual direction of subsequent section is not particularly important. Division around the genu and down the rostrum is performed extraventricularly as far as possible. The rostrum at this point is nearly paper thin, and any remaining fibres are insignificant. No attempt is made to divide blindly the anterior commissure.

Division posteriorly is readily performed following the midline cleft. If an attempt is being made to achieve success with a partial division, it is reasonable to carry the division through approximately the anterior three-quarters. A number of methods have been employed to assure accomplishment of the desired length of section. These include physical measurement of the exposed callosum to be sectioned, identification of structural features (such as the thinning of commissure generally seen in the posterior body or the appearance of the fornices), intraoperative radiographs [122] and, more recently, the image guidance of frameless stereotactic navigational systems. When assurance of section and haemostasis is complete, a metal clip attached to a small piece of Gelfoam may be placed at the posterior extent of the divided callosum; at subsequent surgery, such a marker has often been greatly appreciated when gliosis may obscure the extent of previous resection. It has not created an undesirable, excessive MRI artefact.

Division of the posterior portion of the corpus callosum, either as a second or as an initial procedure, is accomplished in a similar manner. Exposure down the interhemispheric fissure is in this instance facilitated by the deeper falx cerebri. The fibres of the splenium are divided with similar instrumentation, and under magnification the completeness of the section is certain. The underlying arachnoid, beneath which lie the pineal and quadrigeminal cistern, is preserved. The posterior hippocampal commissure may be difficult to distinguish from the overlying callosal fibres, but this is of no practical significance as it is divided as well. If an anterior section has already been performed, the previously placed clip is retrieved. If the posterior section is the initial commissurotomy procedure, a clip is left as a marker at the anteriormost extent of the section.

Closing is performed in the conventional manner. The dura is closed over Gelfilm (Upjohn, Kalamazoo, MI, USA) using 4–0 Vicryl (Ethicon, Inc., Johnson & Johnson, Somerville, NJ, USA) after confirmation of haemostasis. The bone flap is secured with a bone-plating system, the galea aponeurosis is reapproximated using 3–0 Vicryl, and the skin is closed with either 4–0 Prolene (Ethicon, Inc., Johnson & Johnson, Somerville, NJ, USA) or staples. The patient is observed in the neurosurgical observation unit overnight and transferred to the neurosurgical ward the following morning. Mobilization begins immediately, and the patient is typically discharged 3 or 4 days after surgery; in anterior section alone, or in children, hospitalization may be shorter. Anticonvulsant medication is generally left unaltered until at least subsequent follow-up. A decision regarding completion of the callosotomy is usually deferred 6 months or more after the initial procedure.

There are alternative techniques that have been occasionally proposed. Endoscopy [123], stereotactic lesioning [124] and radiosurgery [125–133] have been described, but experience with these techniques for this specific purpose is very limited. Any such technique must be assured of not inadvertently sparing commissural fibres, as suboptimal seizure outcomes have been attributed to such sparing during open procedures. Such techniques must also match the low morbidity and mortality of today's microsurgical procedure.

The utilization of image guidance (neuronavigation) for this surgery has paralleled its increasing incorporation into the majority of neurosurgical operating room environments. Image guidance is routinely used in microsurgery, particularly in epilepsy, and as alluded to earlier it can be a useful aid in callosal section as well. With respect to intraoperative MRI, CT or other updated imaging, the role for these more resource-intensive techniques has not been demonstrated for this procedure. Intraoperative brain shift or deformation is less an issue in either such a central location or in a non-resective procedure.

Refinement of surgical technique has been accompanied by a decrease in the morbidity associated with the procedure. Complications of corpus callosotomy can be considered as surgical or functional in nature [134]. Frontal lobe swelling or infarction with resultant hemiparesis or hemiplegia can result from excessive retraction or sacrifice of bridging veins, and hydrocephalus requiring shunting has been seen with larger surgeries in which there may have been soiling of the ventricular system with surgical debris and blood [10,11]. Current microsurgical technique, with reduced retraction and extraventricular callosal sectioning, has

greatly reduced the incidence of these sequelae. The risk of infection at this time is similar to that of standard neurosurgical procedures.

Transient mutism or decreased spontaneity of speech, with or without mild hemiparesis, has sometimes been noted following anterior callosal section and is presumed to result from either medial frontal retraction or perhaps disconnection [12,135,136]. When it does occur, it almost always resolves within days and is rarely problematic. Posterior section, on the other hand, disrupts interhemispheric transfer of visual, tactile and auditory information, and is responsible for the long-term disconnection syndromes associated with this operation [117,137–141]. Objects presented solely to the hemisphere that is not dominant for language may not be verbally reported by the patient, but as isolation of such stimuli to one hemisphere usually requires a fairly constrained, laboratory environment (e.g. tachistoscopic hemifield visual presentation) it is unusual for this to cause disability. Most patients, as well as many early investigators, have been unaware of the deficit.

Independent and sometimes conflicting behaviours generated by the two hemispheres have been associated with complete callosal section [16]. Anecdotal reports of uncooperative or antagonistic action of the two hands while getting dressed or repeated hesitation about whether or not to enter a room are certainly true, but over time such behaviours generally abate.

The deficit that may arise when an interhemispheric compensatory mechanism that has developed after an earlier hemispheric insult is disrupted by callosal surgery is of greater concern. Mixed dominance, in which language resides in the hemisphere ipsilateral to the dominant hand, may predispose to postoperative language difficulty [142], but this has not been a consistent finding. By a similar mechanism, a pre-existent hemiparesis might worsen following commissurotomy. Fortunately, such deficits are relatively uncommon. The nature of an occasionally observed postoperative memory disturbance remains incompletely understood [117,143].

Conclusion

Commissurotomy may successfully reduce seizure frequency and severity for certain patients who have failed medical management, who are not eligible for resective seizure surgery and who have either preferred not to undergo vagal nerve stimulation or failed to respond to that procedure. Atonic seizures (drop attacks) and secondarily generalized major motor seizures are most likely to be improved, but other seizure types may also respond.

Although early surgeries had often included other anatomical structure, standard commissurotomy today includes only the corpus callosum. Complete callosotomy may not be required in all patients, and anterior three-quarter section, followed by completion of the section if needed, remains a reasonable approach in most patients. As a microsurgical procedure, extraventricular division of the corpus callosum can be safely and assuredly performed. Although there are always numerous variations in surgical technique, the procedure of corpus callosum section is probably less variable than that of most other, longer established surgical interventions for the treatment of epilepsy.

The psychological aspects of commissurotomy have received extraordinary attention in the past [30,81,117,118,136–168], but it is uncommon to encounter permanent disabilities. For the great majority of patients, the benefits resulting from the procedure outweigh any such effects.

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75 Hypothalamic Hamartoma and Multiple Subpial Transection

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Hypothalamic hamartomas

Hypothalamic hamartomas (HHs) are congenital lesions of the hypothalamus often associated with gelastic epilepsy, precocious puberty and behaviour and developmental abnormalities [1–7]. Most cases of HHs are non-familial and sporadic in nature; however, HHs have been reported to be associated with Pallister–Hall syndrome and other congenital syndromes [8,9]. Because HHs are usually small, their presence was often not detected in patients before the advent of magnetic resonance imaging (MRI) [1]. In addition, ictal discharges from HHs are difficult to detect without depth electrodes [2,3,5]. As a result, until recently it was not clear whether HH represented an epiphenomenon of a developmental epilepsy condition or if it was a causal lesion in gelastic epilepsy. Patients with HHs may be asymptomatic, may have gelastic seizures (characterized by brief episodes of laughter) or may have severe generalized epilepsy. The generalized seizures include GTC (generalized tonic–clonic), atypical absence tonic and atonic seizures. With the appearance of these seizure types comes developmental delays and cognitive dysfunction consistent with the Lennox–Gastaut syndrome. Thus, the clinical syndromes of HHs associated with gelastic seizures create a spectrum from occasional gelastic seizures and normal development to severe epilepsy syndromes with developmental delay and precocious puberty. Early attempts to remove HH lesions were disappointing, both in efficacy and from the standpoint of postoperative complications [10–12].

Theories of the aetiology of HHs and their causal role in gelastic and generalized epilepsy and precocious puberty have recently been put forth. Based on genetic findings in Pallister–Hall syndrome, Craig *et al.* [8] reported a possible link between sporadic cases of HHs and somatic mutations in the *GL13* gene. Links between HHs and epilepsy have been proposed by several authors based upon the proximity of HHs to the mammilothalamic tract [2,5,13–16]. Based on combined depth electrode and cortical electrode recordings, Kahane *et al.* [17] proposed a possible mechanism of propagation of seizures in HHs. In their series of five patients, depth electrode recording of gelastic seizures alone showed no activity in the cortical electrodes. Generalized seizures were typically recorded as starting in the hemisphere on the side of the largest portion of the HHs. These generalized seizures did not affect the HHs. These authors and others raise the possibility that this could represent a model for secondary epileptogenesis [2,17]. Although a clear link exists between HHs and gelastic seizures, gelastic seizures are not exclusively linked to HHs. Gelastic epilepsy rarely has been reported to occur secondary to temporal cortical dysplasia [18] and cingulate gyrus lesions [19].

Anatomical classifications of HHs have been proposed based on MRI characteristics and location. Arita *et al.* [20] divided 11 cases into 'parahypothalamic' and 'intrahypothalamic'. This classification was then tested on 61 cases reported in the literature in which an anatomical description was clearly given. The parahypothalamic type described by Arita *et al.* [21] is suspended from the floor of the hypothalamus, may be pedunculated and is more likely to be associated with precocious puberty than with epilepsy. Endocrinological changes leading to precocious puberty have been linked to bioactive substances released by the HHs accelerating the onset of puberty [4]. The intrahypothalamic type, which arises within the hypothalamus itself and may be visible within the third ventricle, is more likely to be associated with epilepsy. MRI characteristics were reported in a series of 72 patients by Freeman *et al.* [22]. They found that HHs were hyperintense to grey matter on T1 in 93% of cases and hypointense on T2 in 74% of cases. MR spectroscopy showed increased myoinositol and reduced *N*-acetylaspartate. HHs always involved the mammillary bodies in their review. Intrahypothalamic involvement was almost always seen and usually pushed the fornix anterolaterally. Larger size was more commonly associated with precocious puberty, as was seen in the series reported by Arita *et al.* [20].

Metabolic imaging of HHs gave further evidence of the causal role HHs play in epilepsy. Positron emission tomography (PET) findings in HHs have been reported by Shahar *et al.* [23]. Ictal PET findings in HHs show increased activity in the region of the hypothalamus. Single photon emission computed tomography (SPECT) findings were reported by Kuzniecky *et al.* [5], and later duplicated by Castro *et al.* [24]. In a series of six patients, Castro *et al.* found all seizure types beginning in the region of the HHs. The mounting evidence of the epileptogenic nature of HHs led to the development of new surgical approaches that have proven safer and more effective in controlling epilepsy related to HHs [5,13,24].

Surgical approaches

Anterior and lateral approaches

The earliest attempts to remove HHs were via the traditional pterional or subfrontal approaches, which gave good exposure

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to any exophytic or pedunculated portions of the HHs, but gave little exposure through lamina terminalis to the intraventricular portion of the HHs and their attachments to the mammilothalamic tracts. It has been proposed that this lack of exposure to the hamartomas' attachments to the circuitry of the mammilothalamic tract accounts for the lack of consistent efficacy of these early surgical attempts. As these approaches must expose and involve critical structures, such as the pituitary gland and infundibulum, cranial nerves and vascular perforating vessels, reports of significant operative morbidity are not surprising. Fohlen *et al.* [25] have suggested a two-stage procedure in which the subventricular portion of the HH is removed via pterional approach and the intraventricular portion is removed at a second stage.

Stereotactic radiofrequency thermocoagulation

Stereotactic techniques have been widely applied to many conditions in neurosurgery, including movement disorders, brain tumour, cyst aspiration, epilepsy depth electrodes, vascular lesions and other functional disorders. Radiofrequency lesioning has been applied to movement disorders, functional disorders and pain conditions such as trigeminal neuralgia [26]. Stereotactic placement of depth electrodes followed by radiofrequency lesioning was reported by Kuzniecky *et al.* [5] in 1997. Radiofrequency lesioning by thermocoagulation was reported by Kuzniecky *et al.* [27] in 2003 in a series of nine patients. Although six patients required repeat lesioning, the authors reported that three patients were seizure free and another four had at least an 80% reduction in seizure frequency. Complications included cranial neuropathy, appetite stimulation and short-term memory disturbance.

Transcallosal approaches

Because of the limited intraventricular view afforded by the pterional and subfrontal approaches, a midline transcallosal approach was proposed by Rosenfeld *et al.* [28]. In their series of HHs, the transcallosal, interforniceal, and the later transcallosal, interforniceal, trans-septal approach was used [29]. In their initial report of five patients, Rosenfeld *et al.* [28] reported >95% resection in all cases with no neurological complications. With a mean reported follow-up of 24 months, three patients were seizure free and two patients had only rare gelastic seizures. Behavioural improvements were also noted. Endocrinological complications of transient diabetes insipidus and enhanced appetite were noted in two patients each. Follow-up reports with larger series were reported by this group [29–31]. Harvey *et al.* [30] reported a series of 29 patients operated on via a transcallosal, interforniceal approach. Greater than 95% resection was achieved in 18 out of 29 patients. With at least 12 months' follow-up and a mean follow-up of 30 months, 15 out of 29 patients were seizure free, with another seven patients achieving Engel's class III or >90% reduction in seizure frequency. Behavioural improvements were seen in most patients. Temporary complications were frequent, with two cases of transient hemiparesis and memory deficits and endocrinological complications noted in one-half of the cases. Permanent complications of short-term memory loss in four, weight gain in five hypothyroidism in five and need for growth hormone supplementation in six patients were reported. Concern for hypothalamic injury leading to hypothalamic syndromes, along with concern for short-term memory deficits, replaced concerns for cranial neuropathy and stroke. A more anterior trajectory approach was developed to avoid forniceal or deep central venous manipulation. This transcallosal, interforniceal, trans-septal approach was reported in 45 patients with reduction in complications related to memory and stroke. Rosenfeld *et al.* [29] suggested that because of possible concern for memory function in some higher-functioning patients, radiosurgery may be preferable.

Success with open surgery for HHs in relieving epilepsy was also reported in a series by Fohlen *et al.* [32]. Twenty-six operations were reported in 18 patients with the primary goal of surgery being disconnection rather than complete removal. In 10 patients, surgery was performed with surgical endoscopy. Hemiparesis was reported in two patients, in one case permanent. The endoscopic frameless stereotactic assisted approach has been reported as the favoured approach by Procaccini *et al.* [33] and Ng and Rekate [6].

Another large HHs surgical series has been reported with both transcallosal resection by Ng *et al.* [34] and endoscopic resection [6]. The transcallosal resection series reported 26 patients with an average follow-up of 20.3 months. Fifty-four per cent of patients were seizure free, with another 35% improved by at least 90%. The majority of patients had improvements in behaviour and cognition. Two patients had permanent memory loss, and two had permanent endocrinological deficits. Patients who were seizure free were more likely to be younger, have smaller HHs, and undergo a total resection. The endoscopic approach was reported in 2007 by Ng in 44 patients [6]. They recommended the endoscopic approach assisted by frameless stereotaxis for cases in which the HH is less than 1 cm, is unilateral and is at least 6 mm below the roof of the third ventricle.

Stereotactic radiosurgery

Steroetactic radiosurgery (SRS) has been successfully applied to a wide variety of intracranial pathologies, including benign tumours, vascular malformations and functional pathologies. SRS uses the same stereotactic principles used in radiofrequency lesioning, but also uses highly conformal radiotherapy. Because of the small size and deep location of HHs and the critical nature of the surrounding anatomy, stereotactic radiosurgery has come to play a role in the treatment of HHs. Initial reports of SRS treatment of HHs involved the use of a gamma knife. The gamma knife uses cobalt-201 source beams of radiation focused on an MRI-targeted lesion. Another technology that may be applied to HHs is linear accelerator based. The linear accelerator uses photons to deliver highly conformal radiation to the lesion. Stereotactic radiosurgery requires the application of a fixed cranial frame and lesion targeting based on MRI localization.

The potential for SRS treatment of epilepsy has been noted based on treatment of epileptogenic lesions with successful control of epilepsy, despite the continued presence of the target lesion [35]. Experimental treatment of epilepsy has shown the potential of SRS to control seizures.

Regis *et al.* [36] reported a prospective multicentre study of gamma knife radiosurgery for mesial temporal lobe epilepsy. Using a dose of 24 Gy at the margin of the mesial temporal lobe target in 21 patients, they reported a 65% seizure-free rate at 2 years' follow-up. Transient complications were commonly reported, but permanent complications were limited to visual field

defects. Several groups have now reported gamma knife treatment of HHs [35,37–41]. Treatment doses averaged at 15 Gy at the 50% isodose line over these series. Regis *et al.* [39,40] have reported the largest series of gamma knife treatment of HHs. In 27 patients treated with at least a 3-year follow-up, they reported a 37% seizure-free rate with an additional 22.2% having only rare seizures. They reported no permanent complications. Based on anatomical classifications, they recommended gamma knife as the primary treatment modality for HHs located primarily in the hypothalamus.

Summary

The understanding of the intrinsic epileptogenic nature of HHs has led to direct and indirect focal surgical treatment. These surgical treatments are evolving with reports of multiple open surgical approaches, stereotactic thermocoagulation and SRS approaches as current options. As hypothalamic hamartomas are variable in their size and location, each of these options will likely have a role in the surgical treatment of medically intractable cases of gelastic and generalized seizures related to HHs. Based upon anatomical factors, a treatment paradigm of surgical resection or disconnection for larger or pedunculated lesions and SRS or endoscopic treatment for lesions located exclusively within the hypothalamus has been offered. Lesions expanding into the third ventricle but limited to one side of the hypothalamus may be reached by the endoscopic approach. Surgical treatment paradigms for HHs will continue to evolve with more surgical experience and longer follow-up with previously treated patients.

Multiple subpial transection

Focal-onset medically intractable epilepsy has been surgically treated for 70 years by location of the seizure focus and resection of the involved cortex. A certain proportion of patients who undergo evaluation for possible surgical resection are found to have an epileptogenic zone originating in, or overlapping with, eloquent cortex. These patients traditionally have been denied surgery because resection of the primary speech, motor, sensory or visual cortex would result in unacceptable deficits. Multiple subpial transection (MST) was developed specifically to address this problem. The purpose of this technique is to disrupt the intracortical horizontal fibre system while preserving the columnar organization of the cortex (i.e. its vertically oriented input and output systems and vascular supply) [42]. The transection of horizontal fibres is aimed at preventing the propagation of epileptic discharges, thus averting the synchronous neuronal activation that ultimately results in the development of clinical seizures. The preservation of the columnar organization of the cortex prevents or minimizes the disruption of the functional state of the transected cortex.

The development of this technique was derived from three sets of experiments, each unrelated to the others or to the field of epilepsy surgery. The first set of experiments by Asanuma and Sakata [43], by Hubel and Wiesel [44] and Mountcastle [45] demonstrated that the vertically oriented micro and macro columns (with their vertically oriented input, output and vascular supply) are the organizational unit of functional cortical architecture. However, the functional role of the intracortical horizontal fibre system is yet to be firmly established. This system is composed of fibres responsible for recurrent inhibition and excitation underlying neuronal plasticity. In the second set of experiments, Sperry [46] demonstrated that surgical disruption of the horizontal fibre system in the visual cortex of the cat, while sparing its columnar organization, does not affect its testable functional status. The third set of experiments was related to the importance of the horizontal fibre system as a 'critical component in cortical circuit necessary for generation and elaboration of paroxysmal discharges' [47]. Epileptic activity in the form of spikes or sharp waves requires a synchronous neuronal activation of a contiguous cortical surface of at least 12–25 mm^2 [47–49]. Tharp [47] found that epileptic foci would synchronize their activity if the distance between them was 5 mm or less, and disrupting the neuropil between the foci would desynchronize the epileptic activity.

With this information, Morrell and colleagues [50] hypothesized that sectioning of the intracortical horizontal fibres at 5-mm intervals, while preserving the columnar organization of the cortex, could abolish epileptic activity yet preserve the functional status of the transected cortex. Testing this hypothesis in the monkey, Morrell produced an epileptic focus with aluminium gel lesions in the left precentral motor cortex, which resulted in the development of focal motor seizures. Using a small wire, he disconnected the horizontal fibres at 5-mm intervals throughout the epileptogenic zone. This procedure, the first subpial transaction for epilepsy, stopped the seizures and no motor deficits were suffered by the monkey from the procedure. To confirm that what he had transected was motor cortex, 1 year later Morrell surgically removed the transected area, resulting in the expected hemiparesis. With this experimental evidence, Morrell and colleagues moved forward into the treatment of intractable human neocortical epilepsy arising in or overlapping eloquent cortex.

Indications for multiple subpial transection

Multiple subpial transection is indicated in any patient in whom the epileptic zone arises from or overlaps with eloquent cortex. The procedure is performed after a detailed presurgical evaluation, which includes closed-circuit television/electroencephalographic recording of habitual seizures using scalp and intracranial electrodes, mainly subdural grids. In addition, detailed functional mapping to identify eloquent cortex by electrical cortical stimulation and evoked potentials is performed. Neuropsychological testing and intracarotid amobarbital tests, as well as functional neuroimaging studies, all assist in defining the baseline function and risks of the procedure. Magnetoencephalography studies have also been very useful in the evaluation of children with an acquired epileptic aphasia of childhood or Landau–Kleffner syndrome (LKS) [51]. It allows more accurate identification of the source of the dipole, especially its depth within a sulcus.

Multiple subpial transection can be performed as the sole procedure or in conjunction with resection of non-eloquent cortex, depending on the extent to which the epileptogenic zone involves eloquent cortex. Most cases of MST occur in conjunction with a cortical resection. Candidates are typically patients with dominant temporal neocortical epilepsy, dominant frontal lobe epilepsy, or primary sensory, motor or visual cortex involvement. In patients

undergoing resection/transection, resection of non-eloquent cortex is performed to within 1.5 cm of the identified eloquent cortex. We recognize that this patient group is problematic for the evaluation of the clinical effectiveness of MST.

Cortical surgical anatomy

Human cortex is arranged in a gyral pattern, which is fairly constant between individuals. However, the microgyral patterns of individual gyri may be considerably variable. These cortical variations must be taken into account in a procedure in which transections are being made perpendicular to the long axis of a gyrus. Thus, careful inspection of each gyrus prior to the procedure is important. Grey matter is, on average, 5 mm thick over the crown of a gyrus. However, the depth of each sulcus is variable.

These points are critical in subpial transection procedures because the objective is to divide the neuropil at 5-mm intervals perpendicular to the long axis of the gyrus while preserving the overlying pia with its blood vessels and the underlying white matter tracts and U-fibres.

About one-quarter of our patients have undergone MST as their primary procedure. These patients mainly had epilepsia partialis continua due to Rasmussen's encephalitis or Landau–Kleffner syndrome. In the patients with Rasmussen's syndrome, the epileptogenic zone arose from primary language and/or motor cortex, whereas in patients with Landau–Kleffner syndrome, it involved posterior language cortex.

Operative procedure

Patients are given preoperative antibiotics and steroids and are positioned so that the surgical site is at the highest point in the operative field. This makes intraoperative electrocorticography (ECoG), resection and transection easier. The head is held in Mayfield head fixation and all pressure points are padded. If the operation is done with the patient awake, the patient's comfort is especially important.

Anaesthesia is accomplished with intravenous methohexital and a generous amount of local anaesthesia. Although methohexital has been shown to activate interictal epileptiform activity, such activation does not extend beyond the epileptogenic zone [52]. Furthermore, the degree of activation of epileptiform activity can be minimized by lowering the infusion rate of methohexital. At our centre, we perform intraoperative ECoG in all cases, even when mapping with subdural grids has been done, to ensure that the initial transections result in the desired abolition of epileptic activity.

Transections

Before performing the transections, careful inspection of the gyri, microgyral pattern, sulci and vascular supply is carried out. Transections are first performed in the more dependent areas to avoid the problem of subarachnoid blood obscuring the other areas. At the edge of the visible gyrus, in an avascular area, a 20-gauge needle is used to open a hole in the pia. The tip of the subpial transection hook is introduced into the grey matter layer and advanced to the next sulcus in a direction perpendicular to the long axis of the gyrus. The tip of the hook is held upward and is visible immediately beneath the pia. It is important that the pia be left undisturbed to minimize vascular injury and scarring. The transection hook is designed with a handle, a malleable shaft and a tip that is 4 mm long (parallel to the cortical width) and 1 mm wide. If the 4-mm tip is introduced just below the pia, it should remain in the grey matter layer, leaving the white matter undisturbed. The tip is angled at 105° and is blunt. These two features make snagging or injuring a vessel less likely. However, it is important to avoid crossing a sulcus where buried vessels are unprotected. While this procedure is simple in principle, we have found that to master it requires considerable experience.

After the first transection is completed, bleeding from the pial opening is controlled with small pieces of Gelfoam and a Cottonoid®. The 4-mm tip is then placed up against the cortex next to the transection so as to select the next transection site, 5 mm from the first. This is repeated until the identified epileptogenic zone is transected. Over a few minutes, the lines take on a striped appearance from the petechial haemorrhages along the lines. Minimal bleeding is encountered if the transections are done properly. EcoG is repeated at the conclusion of the transections. The transected area displays a significant attenuation of the background activity with elimination of the spikes. In cases of persistent epileptiform activity, the possibility that activity is coming from the depth of a sulcus or from remote areas must be considered. On rare occasions, when persistent activity is clearly identified as originating in an area that has been transected, transecting down into the sulcus may be done. To do this safely, the tip of the probe should be turned away from the sulcus as the instrument is advanced.

Favourable outcomes using alternative instruments and methods of transection have been described by other neurosurgeons [53,54].

Seizure outcome

Evaluation of seizure outcome should be carried out in patients who underwent MST without additional cortical resection. We have previously reported our series of patients with partial epilepsy, with 37.5% of patients becoming seizure free at 2 years' follow-up and an additional 37.5% having a worthwhile outcome (classes II and III). However, as has been reported by other centres, there is a late recurrence rate in seizures following MST [54]. Orbach *et al.* [55] reported a relapse rate of 18.6% over several years. Schramm *et al.* (2002) reported on the efficacy of MST alone in 20 patients with drug-resistant epilepsy. One patient had a previous temporal resection; there were two cases each of LKS and electrical status epilepticus of sleep (ESES). In this series, 10% had a class I outcome and 45% had a class II–III outcome. They also noted the relapse in seizures over time [56]. In 2005, Zhao *et al.* [57] treated 80 patients with MST alone as part of their larger series. They reported a 51.7% seizure-free rate in patients with at least 1-year follow-up.

In a meta-analysis of MST with or without additional cortical resection, Spencer *et al.* [58] reviewed 211 patients who underwent MST for intractable epilepsy and found an excellent outcome (greater than 95% reduction in seizure frequency) in 87% of patients with generalized seizures and 68% of patients with simple and complex partial seizures. Zhao *et al.* [57], in the largest series reported to date, reported on 200 patients (80 with MST alone) treated with multiple subpial transection for

intractable partial epilepsy involving eloquent cortex between 1991 and 2000. They reported complete control of seizures in 62.5%, with another 20% of patients having a significant reduction (>75%), with 160 patients having at least a 1-year follow-up [57].

In paediatric patients, Shimizu *et al*. [59] reported on 25 cases in which MST was utilized, with 10 out of 25 having an Engel class I or II outcome. In 2006, Benifla *et al*. [60] reviewed two studies of MST efficacy that included 60 patients (10 with MST alone). They found that between 33% and 46% of patients in each series had Engel class I or II outcomes [60].

Multiple subpial transection had been used to treat Landau–Kleffner syndrome for the past 15 years at our institution. In reviewing 24 patients with classic LKS, Kanner *et al*. [61] found that 13 out of the 24 patients had MST alone and seven had resection and MST. All had continuous spike–wave in slow-wave sleep from a unilateral perisylvian source. All had been followed for at least 2 years. After MST of the perisylvian epileptic abnormality, follow-up revealed that two-thirds of the children could speak in complex sentences at their last formal speech evaluation, with significant improvement of language coming within the first 6 months postoperatively [61].

In 2001, Irwin *et al*. [62] reported five patients presenting with classic LKS who underwent MST. All had ESES clinical seizures, severe language dysfunction or no language and a behavioural disorder. The frequency of seizures and behavioural characteristics were significantly improved in all; however, improvement in language function was not dramatic. This might be related to the duration of the epileptic abnormality prior to surgery [22]. The mean duration was 4.6 years and studies have suggested that a duration of over 3 years is a predictor of the severity of chronic language disturbance [22].

Multiple subpial transection with cortical resection has also been used in patients with multifocal multilobar epileptic foci with clinical seizures and developmental regression. Devinsky *et al*. [63] reported a moderate improvement in language, social and behavioural function with a significant improvement in seizure frequency in this diverse population.

Multiple subpial transection had been used in Rasmussen's encephalitis in seven patients from Morrell's series. In four patients, the targeted seizures were eliminated but the progression of the disease continued. In three out of seven patients, MST did not eliminate the epileptic process due to the fact that it arose from the depth of the sulcus. MST had also been used in patients with refractory status epilepticus that involved eloquent cortex. In both cases, MST successfully stopped the status epilepticus [64].

Surgical morbidity

Acute postoperative morbidity

Cerebral oedema is expected after MST, peaking on the third to the fourth postoperative day. Consequently, patients are expected to experience transient dysfunction of transected cortex, with ensuing neurological deficits lasting for 2–3 weeks. Sometimes mild deficits may persist for several months. Similar observations have been made at the other centres in which MST is performed (see next section on chronic morbidity).

Chronic morbidity

The incidence of chronic morbidity varies, in part, with the experience of the neurosurgeon with the MST procedure. We have reported previously a neurological complication rate of 15%, with 7% suffering a permanent deficit. These deficits included foot drop in 2%, language deficit in 2% and a parietal sensory loss in 1%. Mild but clear diminution in rapid skilled movements was seen in the majority of those undergoing MST of the parietal sensory cortex.

Spencer *et al*. [58], in the meta-analysis of 211 patients, reported the highest morbidity with new neurological deficits found in 19% of those with pure MST, including four with memory decline, five with hemiparesis and one with a partial visual field defect, a total of 23% of the patients with resection and MST had persistent neurological deficit. Schramm *et al*. [56], in the 20 cases of pure MST, reported transient neurological deficit in 29% but all deficits resolved to the point that they would not be noted on a standard clinical examination. In Zhao *et al*.'s [57] larger series of 200 patients, 80 MST alone, transient neurological deficits were reported in just 3%. Likewise, in a review of paediatric MST, Benifla *et al*. [60] reported no permanent language or motor disabilities after MST.

Summary

Multiple subpial transection is successful in the treatment of epilepsy arising or extending into eloquent cortex, both alone or in combination with cortical resection. Its morbidity is low given the area of operation. This procedure allows successful treatment in patients who would otherwise be inoperable. Further refinement and experience with MST will bring additional benefit for patients with medically intractable epilepsy.

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76 Awake Surgery for Epilepsy

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Introduction

Awake craniotomy has been a fundamental surgical technique since the advent of modern neurosurgery. Harvey Cushing [1] performed awake craniotomies for tumour removal using only local anaesthetic. Awake craniotomy, with functional brain mapping and intraoperative electrocorticography (ECoG) recordings, was also fundamental to the pioneering work of Penfield and Jasper [2] as they defined the early neurosurgical interventions for intractable epilepsy. Although advances in anaesthetic and surgical techniques have improved the safety of awake surgery for epilepsy and other neurosurgical disorders, the utility of awake surgery for the majority of patients with intractable epilepsy has been challenged. Improved structural and functional brain imaging, video electroencephalography (VEEG) monitoring, neuropsychological assessments, and outcome measures have led to the delineation of surgically remediable epileptic syndromes [3]. This taxonomic and pathobiological context allows epilepsy surgeons to define operative approaches in advance and to predict more accurately the likelihood of a favourable outcome, in terms of both seizure control and functional status. Contemporary neurosurgeons now have access to preoperative electrographic and semiological (e.g. VEEG) as well as functional data, which have made them less reliant upon intraoperative ECoG and brain mapping than was the case in Penfield's era. These and other advances have prompted a convergence of operative approaches in temporal lobe surgery that emphasize the anatomical resection of mesial structures, with the result that ECoG and brain mapping are used less frequently than in the early days of epilepsy surgery. The challenge is to define the clinical circumstances in which awake surgery may provide value and to use this unique context to optimize the outcome of surgery for each patient.

The two principal goals of surgical intervention for medically refractory epilepsy include the improvement or elimination of seizures and the preservation of neurocognitive functions. These goals have the intention of conferring measurable improvements in the quality of life upon each patient. Assuming proper preoperative patient selection, the resection volume should incorporate the maximum epileptogenic tissue required to produce the elimination or improvement in seizures without the resection of functional or eloquent brain tissue that might create neurocognitive deficits [4]. In the ideal setting, awake surgery techniques allow tailored resections on the basis of intraoperative electrographic and functional data from brain mapping to better achieve these goals.

Contemporaneous with the trend away from awake surgery, advances in anaesthetic and surgical techniques have actually made awake surgery easier and safer. There has also been a continued evolution of functional diagnostic studies that offer more in the way of non-invasive localization of both epileptogenic and eloquent cortices and which may contribute to the utility and efficacy of awake surgery for medically refractory temporal lobe epilepsy (TLE).

In this chapter, we will examine the advances in functional imaging, neuroanaesthesia and neurosurgical technique that have contributed to the utility and efficacy of awake surgery for medically refractory TLE.

Functional assessment

The delineation of eloquent cortex (i.e. language cortex and primary motor and sensory cortex) and the preservation of memory (particularly material-specific verbal memory) are important goals in epilepsy surgery. Over the past 50 years, epilepsy surgeons have relied primarily upon direct cortical stimulation mapping (intraoperative or extraoperative), neuropsychological assessments, and the Wada test to pursue these objectives. The recent introduction of functional imaging and electrographic localization modalities, however, offers surgeons new tools that promise to transform both the preoperative functional analysis and the ultimate execution of the resective surgery.

The traditional assessment of language functions often begins with the intracarotid amobarbital procedure (IAP) or Wada test, developed by Dr Juhn A. Wada in 1949 [5]. Although the Wada test is useful in language *lateralization,* it is insufficient to *localize* language function, which is a prerequisite for surgical intervention. The Wada test is an invasive procedure with definable risks, including carotid artery dissection (0.7%) [6], cerebral vasospasm leading to stroke, hemiplegia, hemisensory loss and unilateral blindness or hemianopsia, as well as femoral neuropathy or haematoma. Additionally, untoward alterations of behavioural and emotional status may occur following amobarbital administration [7–10] during dominant hemisphere injections in patients with frontal lobe pathology or in those with a history of significant emotional trauma. The Wada test has been routinely used to

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assess the risk of material-specific memory losses [11,12], although the efficacy of the Wada test in predicting global memory losses in all patients has been questioned [13,14]. In a few centres, in patients felt to be at risk for memory losses, memory mapping intraoperatively has been used to limit the resection of essential cortex [15] and direct hippocampal ECoG has been performed to limit hippocampal removal [16].

Multiple non-invasive modalities of functional localization have been utilized in recent years, including functional magnetic resonance imaging (fMRI), single photon emission computerized tomography (SPECT), and positron emission tomography (PET) scanning. Although the evolution of these techniques is exciting and each makes important contributions, none, as yet, localizes the epileptogenic zone or eloquent memory and language functions with sufficient clarity to support a surgical approach in all cases.

Although PET imaging has been available for several decades, its utility for the imaging of eloquent brain functions has remained limited in most centres. Radioisotopes such as ^{18}FDG and ^{15}O-water can elucidate regions of altered cerebral blood flow in order to create functional maps of cortical activity. At least two studies [17,18] have directly compared ^{15}O-water PET with Wada testing. Both studies revealed concordance with or even superiority to the language lateralization achieved with the Wada test. PET approaches offer both lateralization and localization and ^{15}O-water PET in both studies provided superior evidence of language localization based on the resulting postoperative deficits. Unfortunately, PET is not available in all centres and ^{15}O-water, in particular, requires the close proximity of a cyclotron.

Functional magnetic resonance imaging has developed as the most promising alternative to Wada testing, both for the assessment of language lateralization and for the prediction of risk for postsurgical global or material-specific memory losses. The superior spatial resolution of fMRI and the lack of radiation exposure are obvious advantages of this technique. Detection of localized changes in cerebral blood oxygen content due to regional brain activations during memory encoding or during the performance of language tasks forms the basis for fMRI assessments of these functions. Comparisons of fMRI and Wada testing have generally demonstrated high concordance between the two modalities [19] and initial studies suggest the possible future utility of fMRI for the prediction of global and material-specific memory losses postoperatively. Localization of essential language cortex is also possible with fMRI. In many studies, similar but non-identical cortical regions are identified by fMRI and direct electrocortical stimulation techniques. fMRI localization of language may vary according to different language testing paradigms that may differentially localize 'language cortex' across the frontal, temporal or parietal cortices. The use of tasks involving object naming based on visually presented definitions [20] has been shown to activate temporal regions better than previously studied paradigms that resulted primarily in frontal activation with poor temporal lateralization. The correlation of these patterns of fMRI task-specific language localization to a practical understanding of the effect of tissue resection in these areas, tantamount to Ojemann's '1 cm rule' [15,21], will be required for these data to provide operative utility equivalent to direct cortical stimulation mapping at surgery.

Other current limitations of fMRI are notable. 'Spurious activations' are not easily distinguished from 'actual activations', as any given activation may or may not be related to the language task being assessed [19]. Also, fMRI signal quality is highly susceptible to motion artefact in patients who cannot remain still. Additionally, fMRI testing is also limited in patients with cranial metal implants (i.e. aneurysm clips, previous craniotomy), pacemakers, claustrophobia and morbid obesity. Finally, patients with high-flow vascular lesions may cause false activation and localization [22]. In patients requiring an extended neocortical resection beyond 'standard' resection volumes, intraoperative brain shift looms as a disadvantage of relying purely upon preoperatively acquired data.

Studies comparing PET versus fMRI [23] and scalp electroencephalography versus fMRI [24] suggest that discrepancies in functional localization are unavoidable with techniques that measure different physiological phenomena during functional testing. These discrepancies may be mitigated when combination modalities are utilized.

An example of a multiple modality assessment used to localize the epileptogenic zone is subtraction ictal single photon emission computerized tomography (SPECT) coregistered to MRI (SISCOM). In a study of 49 patients with medically refractory epilepsy, Anhilde *et al*. [25] used SISCOM in patients with non-lesional epilepsy or poorly circumscribed lesional epilepsy in which VEEG, neurocognitive testing and seizure semiology were non-concordant in the localization of seizure foci for reliable placement of subdural electrodes. In their study, for all patients with favourable outcomes (Engel I–II) at 1 year, SISCOM localization was either prerequisite, or at least in agreement with, other localizing assessments.

Anaesthesia for awake craniotomy

The surgeon's ability to safely and successfully perform awake craniotomies is predicated on a well-controlled anaesthetic technique. Patients must feel minimal pain and discomfort if they are to fully cooperate with functional assessments. Likewise, patients who are oversedated run the risk of respiratory depression, aspiration and airway compromise, which complicates both the surgical approach and attempts at brain mapping.

Proper attention to patient positioning at the start of the assessment is vital to its success and should not be overlooked. Patients should be well padded to avoid compression of neurovascular structures, maximize comfort and limit the urge to move during the procedure. Patient positioning should facilitate communication with the operative team, and frequent reassurances and explanations of the procedure by the operative team enhance patient compliance [26,27].

Awake craniotomy for epilepsy surgery generally incorporates a large scalp incision and craniotomy. This requires a generous scalp and muscle infiltration with local anaesthetic as well as specific nerve blocks, including the lesser and greater occipital, the supraorbital, supratrochlear and auriculotemporal nerves. If Mayfield pin fixation is used then the volume of anaesthetic agent is increased, raising concerns about toxicity [28]. Use of long-acting agents, such as ropivacaine and levobupivacaine, has been

recommended [28] owing to better safety profiles over bupivacaine or lidocaine.

The most commonly used intravenous anaesthetic agent in epilepsy surgery is propofol. It provides rapid anaesthesia and is quickly metabolized, allowing patients to be readily aroused. This is important in awake craniotomies, as the asleep–awake–asleep paradigm is most commonly used, by which patients are kept asleep for the opening of the cranium and dura and are awakened for testing and cortical stimulation. Continuous propofol infusion has been shown to be safe, even with an unprotected airway, as is done in the asleep–awake–asleep model for awake craniotomies for epilepsy surgery [29]. Propofol has a strong antiepileptic effect [30] and may interfere with ECoG; therefore, the anaesthesiologist needs to be aware that the propofol infusion should be discontinued 15–20 min before ECoG [28]. Note that propofol infusion alone does not provide analgesia and manipulation of pain-sensitive structures, such as the dura or cerebral vessels, may cause patient discomfort and poor compliance if an intravenous narcotic agent is not co-administered.

Among the short-acting intravenous narcotic agents, remifentanil appears to be the best suited for awake craniotomies, principally because it allows rapid changes in sedation [28] and is not sequestered in tissues, allowing for very predictable emergence regardless of the duration of infusion [31]. Although it may cause bradycardia in rare patients, one study of 135 patients [32] has shown that the combination of remifentanil plus propofol causes cause less haemodynamic instability than other short-acting narcotics, such as fentanyl.

Dexmedetomidine (DEX), a relatively new, novel intravenous agent, has been gaining acceptance as an alternative (or preferred) choice for neurosurgical procedures that require an awake and cooperative patient. DEX acts as a highly selective α_2-adrenoreceptor agonist, causing effective patient sedation, analgesia and also anxiolysis, but does not depress respiratory function [33]. Unlike other anaesthetic and sedative agents, DEX does not work on the cerebral cortex directly, and provides 'cooperative sedation', with patients easily aroused by verbal command [28,33] and remaining cooperative [33] and cognitively sharp [34,35]. Propofol infusion, in contrast, may leave some patients cognitively blunted or disinhibited with diminished cooperativeness [36,37].

Unlike propofol, DEX incorporates an analgesic effect, thought to be mediated by α_2-receptors in the spinal cord dorsal horn, which inhibit nociceptive signal transmission [38].

Although the degree of analgesia is not on par with intravenous opioids [39], DEX does seem to accentuate the effects of opioids [40] and has been shown to decrease opioid requirements in patients by one-third to one-half [41].

Dexmedetomidine has been demonstrated in adult patients to be particularly effective for use during awake craniotomies for epilepsy [42–46] and may be used as the only agent during the awake portion of the craniotomy [44], without the need for multiple drugs to provide anxiolysis, analgesia and sedation. Limited studies in adolescents for awake craniotomies [47] and for paediatric patients undergoing radiographic testing exist [48,49], suggesting that DEX maybe both safe and effective in these populations, but FDA approval for use of DEX in paediatric patients is still pending.

Dexmedetomidine does not interfere with evoked potential monitoring [50]. Although DEX may minimally alter electroencephalography and ECoG recordings [35,44], it does not significantly affect intraoperative ECoG or cortical stimulation [45] or interfere with ECoG spike activity [46] during awake craniotomy.

Given the positive neurosurgical profile of DEX this novel agent is emerging as highly useful either as an adjunct agent that allows reduction in both narcotic [51,52] and anaesthetic dosing [33] or as the primary agent [45] in awake craniotomies for epilepsy surgeries.

Indications for awake tailored resection for medically refractory epilepsy versus anatomically guided resection

There is little debate regarding the comparative efficacy of surgical intervention for medically intractable epilepsy versus best medical management. The few prospective studies available [53,54], along with multiple retrospective studies, have demonstrated the superiority of surgical treatment in achieving seizure control and improvements in quality of life of treated patients.

However, less is known about the comparative outcomes of various resective approaches, including awake tailored resections versus anatomical resections including standard *en bloc* temporal lobe resection, restricted anterior temporal lobe resection [55] and selective amygdalohippocampectomy [56]. Retrospective comparisons in the 'modern era' [3] suggest that these approaches achieve similar results in terms of seizure freedom postoperatively and do not define the superiority of any particular approach with regard to preservation of neurological and/or language and neuropsychological (especially memory) functions. Many of these studies combine patient subpopulations (i.e. mesial temporal sclerosis, regional and lateral neocortical temporal lobe epilepsies), making definitive comparisons difficult. Given the importance of verbal memory preservation in dominant temporal lobe resections, it has been variably suggested that awake surgery with memory mapping in temporal neocortex [15] or hippocampal ECoG with subtotal hippocampal resection [16] may provide an advantage in preserving memory while assuring a favourable seizure outcome. Additionally, Helmstaedter *et al*. [57] found that a transsylvian approach to the mesial structures resulted in worse material-specific outcomes than a transcortical approach when performed in the dominant temporal lobe.

With the increasing adoption of standardized anatomical resections in contemporary epilepsy surgery, the question of whether awake craniotomy may provide improved seizure control and preservation of language and memory outcomes in selected patients remains to be answered [4]. In the ideal setting, awake surgery with a tailored resection utilizes intraoperative ECoG as well as functional brain mapping to optimize both seizure and functional outcomes in individual patients. This approach is based on two assumptions: (1) that language and memory functions are distributed differentially across the expanse of temporal neocortex in individual patients as documented in numerous studies by Ojemann and others [15,21] and (2) that intraoperatively acquired electroencephalography data provides useful information to guide the volume of resection in selected patients.

A number of retrospective studies suggest that anatomical resective approaches in patients with mesial temporal lobe epilepsy and hippocampal sclerosis provide acceptable outcomes across populations of patients. However, there is still debate as to whether selected patients with a 'non-standard' distribution of epileptogenic tissue or functional (language or memory) cortex might benefit from an approach that incorporates awake surgery, intraoperative ECoG and functional brain mapping approaches.

Intraoperative ECoG addresses the first aim of epilepsy surgery, improvement of seizure control, whereas functional mapping is targeted at avoiding postoperative language, memory and motor deficits. In principle, preresection ECoG findings are useful to guide the extent of resection, whereas the postresection ECoG provides information that can be used to decide whether or not to resect more tissue or even to predict the ultimate seizure outcome of surgery. Some studies in awake patients suggest that the ECoG is predictive of seizure outcome, particularly if spikes are either absent preresection or particularly abundant post resection [58,59]. Other studies, in the context of anatomical, measured resections with maximal mesial resection found no correlation of ECoG with seizure outcomes [60,61]. For example, Schwartz *et al*. [60], in their prospective study of 29 patients undergoing a standardized anatomical resection under general anaesthesia, found no correlation between preresection or postresection ECoG data and seizure outcome. In contrast, in a prospective series of 140 patients at the University of Washington, McKhann *et al*. [16] found a positive correlation between residual postresection ECoG spikes in the hippocampus and a worsened seizure outcome. Of interest, however, the study did not show a correlation between residual postresection spiking in either cortical or parahippocampal regions and worse outcomes. It has been argued, and is important to consider, however, that although preresection data may be predictive of seizure outcome, knowing this information does not improve seizure outcome and, by extension, may not, by itself, justify awake surgery.

Awake functional mapping addresses the second goal of epilepsy surgery: to preserve eloquent (language and memory) brain functions while optimizing resection volume to improve seizure outcome. Ojemann *et al*. [15] suggested that up to 17% of patients undergoing a 'standard' anatomical dominant temporal lobe resection (4.0–4.5 cm) without mapping would experience postoperative deficits; furthermore, a study of patients undergoing a smaller, standard anatomical resection in the dominant hemisphere [62] documented a 7% permanent postoperative language deficit. Such data, combined with Ojemann's demonstration, in large numbers of patients, of significant interpatient variability in language representation across the temporal neocortex, and the '1 cm rule' (which describes enduring deficits in patients with resections within 1 cm of essential language areas) suggest that awake surgery with mapping may be useful in selected patients [15,21].

'Positive' language mapping, in which regions of essential language cortex are localized with electrocortical stimulation, has provided the gold standard technique of language mapping over many decades [15,63]. Recent data acquired in non-epileptic patients with malignant brain tumours [64] suggest that a 'negative' language mapping technique, in which the absence of language representation in a cortical area is determined, may be sufficient to allow a safe resection in these patients. Given the likely differences in the cortical organization of language in patients with intractable epilepsy and with adult-onset brain tumours, particularly in the superior temporal gyrus [63], the use of 'positive' language mapping may be more appropriate in patients with intractable epilepsy, whereas 'negative' mapping may be sufficient in the setting of a brain tumour resection.

In addition to language mapping, functional mapping of material-specific memory may be helpful in minimizing postoperative material-specific memory deficits, which can be more debilitating than the original disease under treatment [65]. Both the lateral temporal neocortex and the hippocampus are felt to contribute to the input and encoding of verbal memory [56,66]. Given that pure lateral or neocortical temporal lobe epilepsies (with no mesiobasal involvement) account for approximately 10.7% of patients with medically refractory TLE [67], and that many patients with medically refractory TLE have some evidence of involvement of both mesiobasal structures and the lateral temporal neocortex, functional mapping of verbal memory function may be useful in these patients.

Finally, there has never been a direct comparison of anatomical resections versus awake tailored resections in a prospective randomized study. Until such a time comes, it will remain impossible to champion one approach strictly over the other. And such a study may very well not be either practical or useful as, in fact, most epilepsy surgeons will continue to utilize both techniques, tailoring their approach to the individual patient, as seems appropriate.

Technical aspects of temporal lobe resection tailored to intraoperative recording and stimulation

Awake surgery with intraoperative functional stimulation mapping is surprisingly well tolerated by most patients. Since 1990 we have performed awake surgery with brain mapping on over 350 patients between the ages of 8 and 67 years. Extensive patient preparation for the procedure, an experienced operative team including a specialized nurse practitioner, a neurophysiology technical staff and improved anaesthetic techniques all have contributed to the success of these procedures.

Preoperative preparation

Before embarking on awake brain surgery, patients are instructed as to the experience of awake surgery and brain mapping, which includes viewing a video of this procedure. In the outpatient setting, preceding surgery, each step of the procedure is explained in detail, all questions are answered and the patient is incorporated as a critical member of the operative team. The patient is presented with a set of 80 object images, projected for 4 s each, and each one requiring the patient to read a short phrase and name an object. The images that the patient has difficulty with are removed from the list. A selection of objects that the patient can reliably and accurately name is identified for use during surgery. A major goal of this encounter is to make the patient

comfortable with the operative procedure and to optimize compliance during the various stages of the operation [26].

Anaesthetic technique

On arrival in the operating theatre, anaesthesia is administered before placement of the Foley catheter, patient positioning and cranial fixation, and is then is continued until the dura is opened. Under most circumstances, the patient will be awake and responsive within 5–10 min of discontinuation of the intravenous infusion. After the 30–60 min required for ECoG and stimulation mapping, the infusion is restarted and the patient re-anaesthetized until the completion of the operation.

Premedication and positioning

Before surgery, patients receive intravenous dexamethasone (10 mg i.v.), prophylactic antibiotics and an adequate dose of anticonvulsant medication (i.v. or p.o.) to assure therapeutic levels during the operation. The head is clipped with an electric shaver and electroencephalography reference electrodes are placed. Benzodiazepines are not used for premedication in order to assure the fidelity of the ECoG. The patient is placed on the operating table with appropriate padding. Pneumatic compression stockings and a Foley catheter are placed, and mannitol (0.75 g/kg), plus or minus furosemide (20–40 mg), is administered. The patient is placed in a modified lateral decubitus position with appropriate padding but no axillary roll. Although the head can be placed on a foam doughnut without fixation, our current preference is to use a Mayfield three-point fixation device with strategic injections of local anaesthetic (lidocaine 0.25% and bupivacaine 0.25%) at the pin sites before placement. The lateral position and slight neck extension usually assure airway patency during the period of deepest sedation. Occasionally, however, a nasal trumpet is required during this period but is usually removed during language mapping so that it does not impede the patient's speech.

Local anaesthesia

For a standard temporal lobe resection, a large question mark scalp incision is used – of sufficient size to allow exposure of the hand motor cortex, Broca's area, Wernicke's area and the entire temporal lobe. Before the skin incision, local anaesthetic (lidocaine plus bupivacaine, 0.25%, final concentration, 30–45 mL^3) is injected as follows: (1) nerve blocks, via targeted injections with a 30-gauge needle in the distribution of the supraorbital, auriculotemporal and greater occipital nerves; (2) a field block, created by connecting these three sites with a series of injections to surround all but the medial aspect of the incision; (3) an incisional block, via subcutaneous injection along the entire incision with a 27-gauge needle; and (4) a deep muscle block via injection directly into the temporalis muscle over the pterion to reduce pain from muscle retraction.

Craniotomy

The question mark scalp incision is fashioned and the unitary scalp/muscle flap is dissected and retracted anteriorly to optimize exposure of the anterior temporal lobe anterior to essential language sites. The first burr hole is placed over the pterion and local anaesthetic is injected with a 30-gauge needle within the leaves of the dura surrounding the middle meningeal artery. Additional burr holes are placed centripetally and a side-cutting saw is used to connect them. A high-speed drill is used to complete the saw cut over the anterior temporal squama and the flap is removed. The inferior temporal squama is rongeured to the middle fossa floor over a distance of 6 cm and all air cells are thoroughly waxed. The skull clamp that will be used to hold the ECoG halo is positioned in the frontal–medial aspect of the craniotomy. The dura may be somewhat tense at this point as a result of hypoventilation and high P_{CO_2}; therefore, prior to dural opening, the patient is usually wakened and instructed to hyperventilate to relax the brain and the overlying dura.

Intraoperative electrocorticography

The goal of intraoperative EcoG recording during surgery is to assist in the delineation of the epileptogenic region. This is described as the volume of tissue that is necessary and sufficient to produce habitual spontaneous seizures [68]. In Penfield's time, the pattern of distribution of interictal spikes on the scalp EEG and during direct cortical recordings at surgery was relied upon to determine the appropriate resection volume [2]. In contemporary practice, the epileptogenic region is identified by a combination of factors, which includes (1) the spatial distribution of interictal spike discharges and the zone of ictal onset, determined through VEEG recordings; (2) the location of epileptogenic lesion(s) revealed by structural imaging [foreign tissue, neuronal migration disorder, mesial temporal sclerosis (MTS), etc.]; and (3) the extent of non-epileptic focal functional deficits determined by the neuropsychological assessment and functional imaging [69]. The role of interictal spikes (IISs) identified on intraoperative ECoG in the determination of the volume of tissue resection is less prominent in current practice, and these data must be considered within the context of the global dataset and the surgically remediable syndrome of each patient.

In a typical patient with mesial temporal lobe epilepsy (MTLE) with a history of early injury, imaging showing hippocampal atrophy and sclerosis, and exclusively unilateral IIS from scalp recordings, characteristic ECoG abnormalities are often identified in anterior and mesial structures via subtemporal strip electrodes. In such patients, a standard, anatomically defined (non-tailored) anterior temporal resection will produce a favourable outcome from the standpoint of seizure control. If this resection avoids the superior temporal gyrus, limits the middle gyrus resection to 2.5 cm and incorporates an anatomical removal of mesial structures then preservation of language functions will usually be satisfactory [62,70].

Our recent institutional experience suggests, however, that a growing minority of patients do not have classic MTLE but may have regional epileptogenic zones (i.e. mesial and lateral) or exclusive lateral neocortical interictal foci and ictal onsets [lateral temporal lobe epilepsy (LTLE)] [67]. Many of these patients with neocortical TLE may have no evident abnormality on MR scans. ECoG recordings will reveal widespread or multifocal discharges or exclusively lateral discharges in patients with neocortical LTLE. In such patients with regional or lateral temporal lobe epileptogenic regions, intraoperative ECoG and functional mapping may permit the resection to be extended beyond standard boundaries in order to incorporate more of the epileptogenic region. In these patients,

the outcome may be improved with the resection of an epileptogenic region that goes beyond standard anatomical boundaries.

Electrode placement and ECoG#1

In our standard ECoG protocol, we sample the activity of the orbitofrontal and subtemporal neocortex with four four-contact subdural strip electrodes. These are positioned with one beneath the frontal lobe and three beneath the temporal lobe, each inserted with a lateral–medial trajectory. In the temporal lobe, the medialmost contacts lie beneath the uncus anteriorly and the hippocampus/parahippocampal gyrus in the more posterior positions. These are inserted gently to avoid inadvertent rupture of subtemporal bridging veins. The halo electrode holder with carbon-tipped electrodes is now placed on the skull clamp and the surface electrodes are lowered to the cortex. Generally, three are placed above the Sylvian fissure over the frontoparietal operculum and three each over the superior and middle temporal gyri. The patient's arousal from sedation should now be complete and the initial recording commenced.

During a 10- to 15-min awake tracing, the distribution of interictal discharges, slowing and voltage suppression is sampled over the lateral and subtemporal cortices. A sleep tracing with a characteristic activation of discharges in selected patients may be simulated via a methohexital bolus, which produces a burst suppression ECoG effect initially, followed by the activation of spike discharges as the methohexital dissipates and the tracing returns to a normal awake pattern. This effect has also been observed with propofol during the transition into and out of the waking state and maybe useful to identify spike foci that may not appear during the exclusively waking state. At the end of the recording, the distribution of spike discharges over the neocortex is noted for subsequent comparison with the localization of eloquent cortical regions.

Stimulation parameters

In our centre, cortical stimulation is performed using bipolar constant-current cortical stimulation, applied across two 1-mm stainless-steel ball electrodes separated by 0.5 cm. Stimulus parameters incorporate 60-Hz trains of biphasic pulses, each phase being 1 ms in duration. In the rolandic region, 'positive' responses are noted (i.e. a movement or a reported perception of a sensation), whereas in language cortex 'negative' responses are typical (i.e. interruption or alteration of reading or object naming).

Motor and sensory responses are usually elicited with currents of 1–4 mA applied for 4-s or until a positive motor or sensory response is obtained. In language cortex, a current that is 1 mA below the lowest determined afterdischarge (AD) threshold is utilized during the 4-s presentation of an object image for the patient to name. The AD threshold is determined by the application of a 4-s stimulus to the cortex adjacent to a carbon-tipped surface electrode. Stimuli of increasing current density are applied until a localized electrical seizure is obtained, usually in the 6–12 mA range. The AD threshold is evaluated across the exposed region of temporal neocortex and parietal operculum, and across the inferior and middle frontal gyri anterior to the face motor cortex. This threshold may vary across the expanse of normal cortex and within, or adjacent to, areas of cortical injury, gliosis, malformation or foreign tissue lesions, where the AD threshold may be unusually low and where prolonged focal electrical seizures may be produced at relatively low currents. Language mapping is then commenced at a current of 1 mA lower than that required to elicit an AD. This current is felt to be large enough to abrogate the function of a discrete volume of cortex through a depolarization blockade, but not so large as to produce a propagating seizure that would affect distant areas. The applied current may have to be altered during language mapping, depending on the cortical responses. If prolonged ADs are elicited then the current may need to be reduced. If no interference with language function is produced, it may need to be increased to the level of the AD threshold.

Motor and sensory mapping

Motor mapping is undertaken first, starting with low currents (i.e. 1.0–1.5 mA) to avoid iatrogenic production of a focal motor seizure or convulsion. Should intraoperative seizures develop, methohexital is administered for abortive seizure therapy. The patient is asked to protrude the tongue and the tongue motor area is identified through observation of tongue deviation. Observation of face and hand movements by an assistant further defines the motor homunculus. Over the sensory cortex, tingling sensations are reported over the appropriate body region. Occasionally, at low currents, the patient may report a sensory experience from the motor area and at higher currents a motor response from the sensory area. Normally, 2- to 4-mA currents are required to elicit robust motor and sensory responses. Numbered (1–10) paper tags are placed over the rolandic cortex for precise identification of functional areas. This region, however, should be avoided during language stimulation that utilizes higher currents, as this could elicit a generalized seizure if such currents are applied to the motor cortex.

Language mapping

The goal of language mapping is to identify essential language sites in the temporal lobe to permit a maximal tailored resection of epileptogenic tissue without adversely affecting language function. A low baseline naming error rate is essential to the mapping procedure and only objects that the patient can reliably name are utilized.

Before language mapping, 20 sterile numbered tickets are placed over the exposed cortex to be mapped. Using a slide projector, images of common objects are presented for 4 s to the patient to name while current is applied to cortex adjacent to each ticket. Over 10–20 min, all ticketed areas of cortex are sampled several times with two objectives: (1) the identification of 'positive naming sites', stimulation of which produces an alteration in naming function ('positive mapping') and (2) the careful sampling of the region of desired cortical resection to ensure that only 'negative sites' (in which no alteration of naming occurs with maximal stimulation) will be incorporated into the resection volume ('negative mapping'). It is our practice to expose a large expanse of temporal–parietal cortex with the craniotomy, as positive language sites may be 8–10 cm posterior to the temporal tip. If these sites are clearly identified then a more aggressive resection of lateral cortex may be undertaken with observation of the '1 cm rule'. Although we thoroughly sample the volume of desired resection to ensure that only 'negative sites' are resected,

as previously noted, we do not rely solely on 'negative mapping' techniques alone to guide a tailored resection of tissue, as has been recently proposed in the context of glioma surgery [64]. If no positive sites can be identified, our approach is to stimulate the region of proposed resection with threshold or suprathreshold currents during language mapping to assure that no positive sites are present and to have the patient actively naming during the resection of lateral neocortex.

Lateral cortical resection: ECoG#2 and hippocampal removal

The lateral cortical resection undertaken is tailored to the results of the ECoG and language mapping. The inferior temporal and fusiform gyri are resected and the ventricle is entered and slit open to expose the entirety of the hippocampus in preparation for ECoG#2. Four four-contact electrodes are placed: (1) under the orbitofrontal cortex; (2) within the temporal horn of the ventricle in an anterior–posterior trajectory with contacts on the surface of the hippocampus; (3) under the parahippocampal gyrus parallel to the hippocampal electrode; and (4) under the posterior temporal cortex running from lateral to medial. Carbon-tipped surface electrodes are placed on the exposed regions of temporal and suprasylvian neocortex. After the ECoG recording, the hippocampal and incremental tailored neocortical resections are completed. Some studies have suggested that tailoring of the hippocampal resection based on ECoG findings may permit a subtotal hippocampal resection with favourable seizure outcome [16]. Our practice is to pursue a total hippocampal removal, assuming that our preoperative multivariate analysis of neuropsychological, imaging and electrographic parameters predicts a favourable outcome with regard to verbal memory [12].

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77 Epilepsy Surgery in Children

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Introduction

Although neurosurgical intervention for medically refractory epilepsy has been utilized in adults for over a century, surgical treatment for children began in earnest only 20 years ago. The goal of surgical treatment is to eliminate seizures as quickly and early in brain development as possible while minimizing adverse effects. Seizure control early in cerebral development is important to ensure optimal cognitive and functional outcomes [1]. In this chapter, the concepts of paediatric epilepsy surgery are reviewed with an emphasis on literature published in the last 10 years. The chapter starts with an appraisal of treatment-resistant epilepsy and emphasizes the neurodevelopmental consequences of suboptimal seizure control. This is followed by the presurgical evaluation and surgical management of patients with paediatric epilepsy. Finally, an analysis of surgical outcomes with regards to seizure control, complications, cognitive development and quality of life is described. The objective of this chapter is to assist the paediatrician and neurologist in understanding the rationale behind early diagnosis of therapy resistance and, when appropriate, referral to paediatric epilepsy centres for comprehensive evaluation and possible surgical treatment.

Therapy-resistant epilepsy and the rationale for early seizure control

Which children are surgical candidates?

Epidemiological studies show that the incidence of new-onset seizures in children reaches four cases per 1000 of the population. Other studies point out that once a child has failed to obtain seizure control after trying two to four antiepileptic drugs (AEDs), the probability that additional medications will stop seizures in the long term is under 5% [2]. If the child presents with an identifiable epileptogenic structural lesion on neuroimaging, the possibility that additional medications will help is even lower [3]. These findings allow primary care physicians to identify children with 'therapy-resistant' epilepsy early in the course of their disease, who should be referred to a specialty paediatric epilepsy centre where surgery is one therapeutic option. Exhaustive attempts at trying all available AEDs before referring a child to a specialty epilepsy centre is suboptimal care.

Population studies indicate that approximately 8–10% of children with newly diagnosed epilepsy will have medically refractory seizures when followed over 2 years. Refractory seizures have been defined as seizures persisting after use of more than two AEDs at a frequency of one or more per month [4]. Of those children medically controlled at 1 year, an additional 8% will meet the criteria for intractability when followed to 2 years. Hence, children need to be followed closely, as some who are initially controlled on AEDs will become medically refractory. In addition to response to AEDs, the type of epilepsy syndrome predicts which children are most likely to become therapy resistant. *Symptomatic* epilepsy refers to children in whom seizures are secondary to a structural brain abnormality. The symptomatic group constitutes approximately 20% of children with new-onset epilepsy. Symptomatic epilepsy has lower remission rates with medical therapy. Aetiologies include mesial temporal sclerosis, cortical dysplasia, tuberous sclerosis and tumours. Patients with certain aetiologies such as hippocampal sclerosis, cerebral dysgenesis and dual pathologies have a particularly poor prognosis, with a 11–35% chance of becoming seizure free with medications [5,6]. *Idiopathic* epilepsy refers to children in whom seizures are the only manifestation of this disorder. Idiopathic epilepsies can be localization related (e.g. benign rolandic epilepsy) or generalized, and are presumed to be genetic in origin. These children constitute 30% of new-onset paediatric epilepsy patients and, when the onset is from 5 to 9 years of age, they have high remission rates with medical therapy. *Cryptogenic* epilepsy accounts for approximately 50% of new-onset seizure cases for which no aetiology has been determined with current diagnostic methods. There is a great deal of clinical and scientific interest in the cryptogenic group, as the aetiology may range from polygenic to subtle microstructural lesions as yet unidentifiable by current neuroimaging techniques. It is hoped that in the future the cryptogenic group is reduced in size as a result of better diagnostic approaches.

Of children with medically refractory epilepsy, most have cryptogenic/symptomatic generalized epilepsy, 11% have localization-related cryptogenic/symptomatic epilepsy and 3% have idiopathic epilepsy [4]. Factors such as high initial seizure frequency and focal electroencephalography findings are reported to be associated with a higher risk of becoming medically intractable [7]. Mental retardation, neurological abnormality, positive neuroradiological findings, perinatal anoxia, neonatal convulsion, history of status epilepticus and symptomatic aetiology are other risk factors for the development of refractory epilepsy in children. Age at seizure onset, status epilepticus, mixed type of seizure disorder and history of frequent seizures (more than once per month) are reported as additional independent risk factors for the development of refractory epilepsy in children.

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Response to AEDs varies by clinical seizure category. Approximately 55% of children with idiopathic epilepsy will experience remission after 1 year. An additional 40% of children with idiopathic epilepsy will have less than one seizure per month. Thus, 95% of children with idiopathic epilepsy experience near-seizure control with medication. Cryptogenic cases can also expect a good response to medical treatment, with a total of approximately 92% achieving near-seizure control within 2 years. Although symptomatic partial seizures have an approximately 71% rate of remission within 2 years, early-onset symptomatic/cryptogenic generalized epilepsy has a 47% rate of seizure control [8]. Many children considered for epilepsy surgery fall into this latter group of patients with symptomatic epilepsy. A meta-analysis has shown that the development of new AEDs has not significantly impacted the percentage of patients seizure free with medications [9]. This is an important finding, as approximately 16% of children with new-onset epilepsy will be medically intractable and, of those, approximately 50% will have symptomatic epilepsy. Overall, an estimated 10% of children with new-onset epilepsy will likely be both symptomatic and therapy resistant. This is calculated based on the 20% incidence of symptomatic epilepsy with 50% remission rate.

Seizure presentation in children is not the same as in adults. In infants and young children, symptomatic epilepsy from unilateral lesions may manifest as generalized seizures. Children with symptomatic epilepsy often do not present with a clear MRI abnormality (e.g. tumour or vascular malformation) with congruent electroencephalography findings and semiology. Many times children present with severe generalized seizures by semiology and electroencephalography, including infantile spasms, and will have unilateral focal or hemispheric lesions on MRI. It is also common to find focal electroencephalography findings and negative MRI, although there may be an underlying focal cortical abnormality causing the seizures. False-negative MR scans occur because cortical dysplasia is difficult to identify in a young child's brain scan due to brain growth and myelination of white matter tracts in the first 2 years of life. Furthermore, children with multiple brain lesions, as with tuberous sclerosis, can have electroencephalography localization to one of the tubers and be a surgical candidate with the potential for excellent seizure control. Finally, infants with unilateral hemispheric disease, such as Rasmussen's syndrome, hemimegalencephaly and severe cortical dysplasia, may have generalized seizures and bilateral abnormalities detectable by electroencephalography but are extremely amenable to surgical treatment [10]. Because of the variability in clinical presentation, referral to a paediatric epilepsy specialty centre is recommended for children under age 2 years with uncontrolled seizures in order to determine the aetiology and formulate an effective treatment plan [1].

Risks of uncontrolled epilepsy

Why is it critical to control seizures as soon as possible in infants and children even if that means resective surgery?

Inadequately controlled epilepsy in infants and children poses significant neurodevelopmental ramifications. These consequences span cognitive, behavioural, psychosocial and psychiatric realms. One study looking at children with unilateral temporal lobe epilepsy found that preoperative intellectual dysfunction (IQ < 79) was present in 57% of children [11]. The incidence of intellectual impairment was approximately 83% in children with epilepsy onset in the first year of life. The notion of epilepsy-induced intellectual deterioration, termed an *epileptic encephalopathy*, is congruent with other studies that have shown that intractable seizures during the first 24 months of life, especially when occurring daily, are a risk factor for severe mental retardation independent of aetiology [12]. In medically intractable infantile spasms, impaired cognition, language and social/communication abilities (similar to autism) are almost guaranteed to develop if adequate early treatment is not implemented [13]. These findings support the notion that seizure control during the early years of brain growth is critical for intellectual development. Contemporary work suggests that early surgical intervention may result in improved IQ scores and developmental indices [14–17]. Additionally, adolescents with intractable epilepsy can expect to have poorer psychosocial outcomes than those patients whose epilepsy is controlled [18]. Patients with a childhood history of epilepsy have lower rates of high school completion, employment, marriage and overall socioeconomic productivity. Considerable consensus exists among paediatric neurologists and neurosurgeons that the prevention of developmental decline is paramount in the treatment of paediatric patients with refractory epilepsy [1].

Seizure-related morbidity and mortality is also important to consider when discussing the rationale for early surgical intervention. Children with refractory epilepsy are at risk of seizure-related morbidity and mortality compared with children without seizures [19,20]. The mortality risk from uncontrolled epilepsy is 0.5% per year and accumulates over a lifetime, making it particularly relevant in young children. Causes of seizure-related mortality include sudden unexplained death in epilepsy (SUDEP), aspiration pneumonia, trauma and status epilepticus.

Surgical therapy, in appropriate symptomatic cases, should be considered as an option in the management of children with therapy-resistant epilepsy early in the course of their epilepsy disorder. The goal of surgery is to prevent catastrophic developmental arrest or regression by stopping the seizures. Additionally, the functional plasticity of the infant brain allows for neurological recovery and reorganization after surgical treatment. Finally, optimal seizure control may improve or normalize psychosocial function and quality of life. The evaluation and treatment of intractable paediatric epilepsy is complex and requires a multidisciplinary team approach with unique clinical expertise. Thus, referral to a specialty paediatric epilepsy centre for evaluation is an essential early step in the management of infants and children with therapy-resistant epilepsy.

Symptomatic substrates in surgically treated children

The most common histopathological finding in children undergoing epilepsy surgery is cortical dysplasia (Table 77.1) [21]. Cortical dysplasia can be severe or mild, focal or involve most of the cerebral hemisphere (Fig. 77.1). Cortical dysplasia is a congenital structural abnormality consisting at a minimum of cortical dyslamination and columnar disorganization [22]. Severe cortical

dysplasia consists of cortical dyslamination plus the presence of abnormal cells in the cortex and subcortical white matter termed *cytomegalic neurones and balloon cells* [23]. Evaluation of children with cortical dysplasia by structural MRI may present challenges, as the radiographic abnormalities may be subtle or undetectable in 20–30% of cases. Other neuroimaging studies may be necessary to detect cortical dysplasia, including FDG-positron emission tomography (FDG-PET), magnetoencephalography (MEG) and ictal single photon emission computerized tomography (ictal-SPECT). Cortical dysplasia may be localized most commonly in the frontal and temporal lobes, be multilobar or involve an entire hemisphere (Fig. 77.1). Larger dysplastic lesions detected by MRI, with more severe histopathology, are typically present in patients who have early-onset epilepsy.

Low-grade neoplasms, such as gangliogliomas and dysembryoplastic neuroepithelial tumours (DNETs), make up the next most frequent aetiology in paediatric epilepsy surgery patients (Fig. 77.2A and Table 77.1). Tumours are the second most common aetiology behind hippocampal sclerosis in adult epilepsy surgery populations. Complete resection of these tumours typically results in high seizure remission rates [24]. Children who suffer brain damage from perinatal strokes or bacterial/viral infections constitute another group that is treated surgically for refractory epilepsy (Fig. 77.2B and H). Hippocampal sclerosis, which is the most frequently encountered pathology in adult patients undergoing epilepsy neurosurgery, is an infrequent cause of pharmacoresistant seizures in children (Fig. 77.2E).

Table 77.1 Aetiologies in patients undergoing paediatric epilepsy surgery under the age of 18 years

Aetiology	Cases (%)
Cortical dysplasia	38
Focal	25
Multilobar	13
Tumour	19
Atrophy/stroke	10
Hippocampal sclerosis	6
Tuberous sclerosis complex	5
Hemimegalencephaly	4
Hypothalamic hamartoma	4
Sturge–Weber	3
Rasmussen encephalitis	3

Modified from ref. 21.

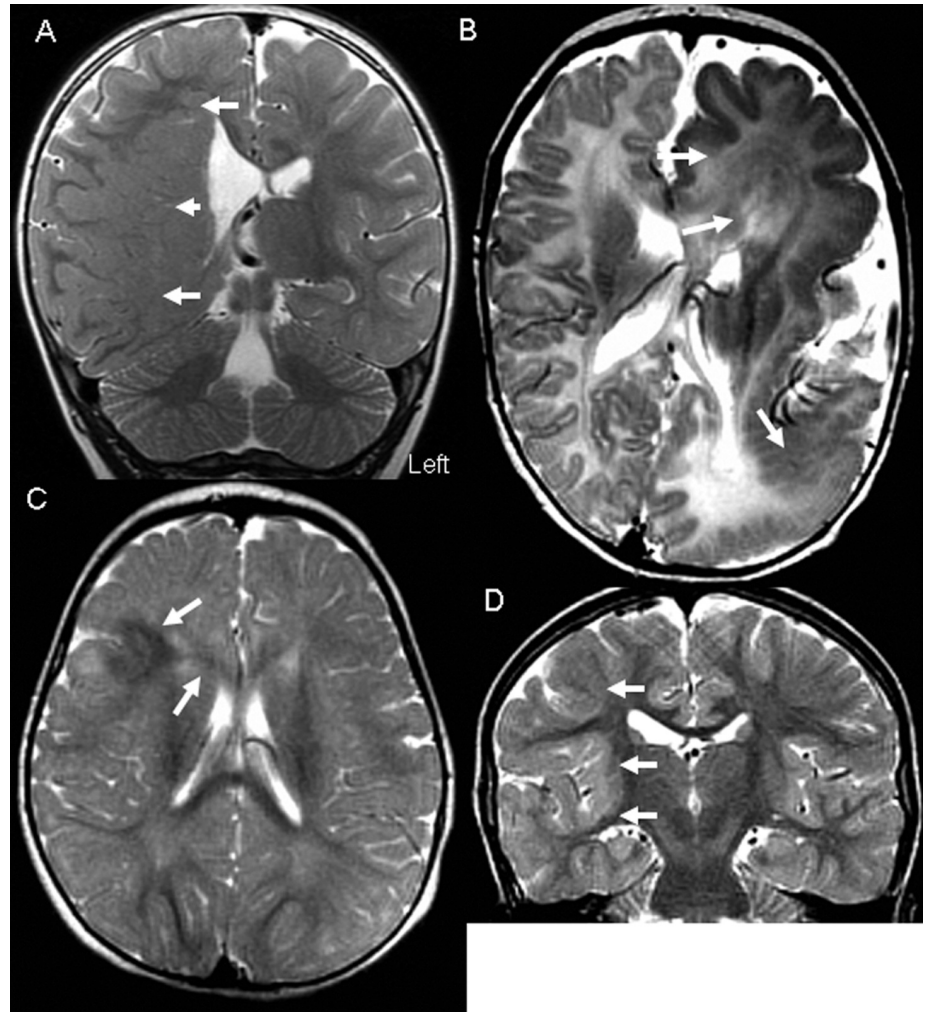

Fig. 77.1 MR scans of cortical dysplasia. (A) Example of severe right hemispheric cortical malformation from a large heterotopia (arrows). Notice the abnormal lateral ventricle, displaced or missing right basal ganglia and thalamus, and obliterated right temporal horn and hippocampal formation. (B) Example of a left hemimegalencephaly (arrows). Notice that the left cerebral hemisphere is larger than the right. (C) Example of a focal right frontal cortical dysplasia that extends to the ventricle (arrows). (D) Subtle cortical dysplasia of the right hemisphere. Note the decreased T2 white matter signal of the right frontal and temporal cortex and thicker insular cortex (arrows). Pathology confirmed Palmini type IIA cortical dysplasia (severe without balloon cells).

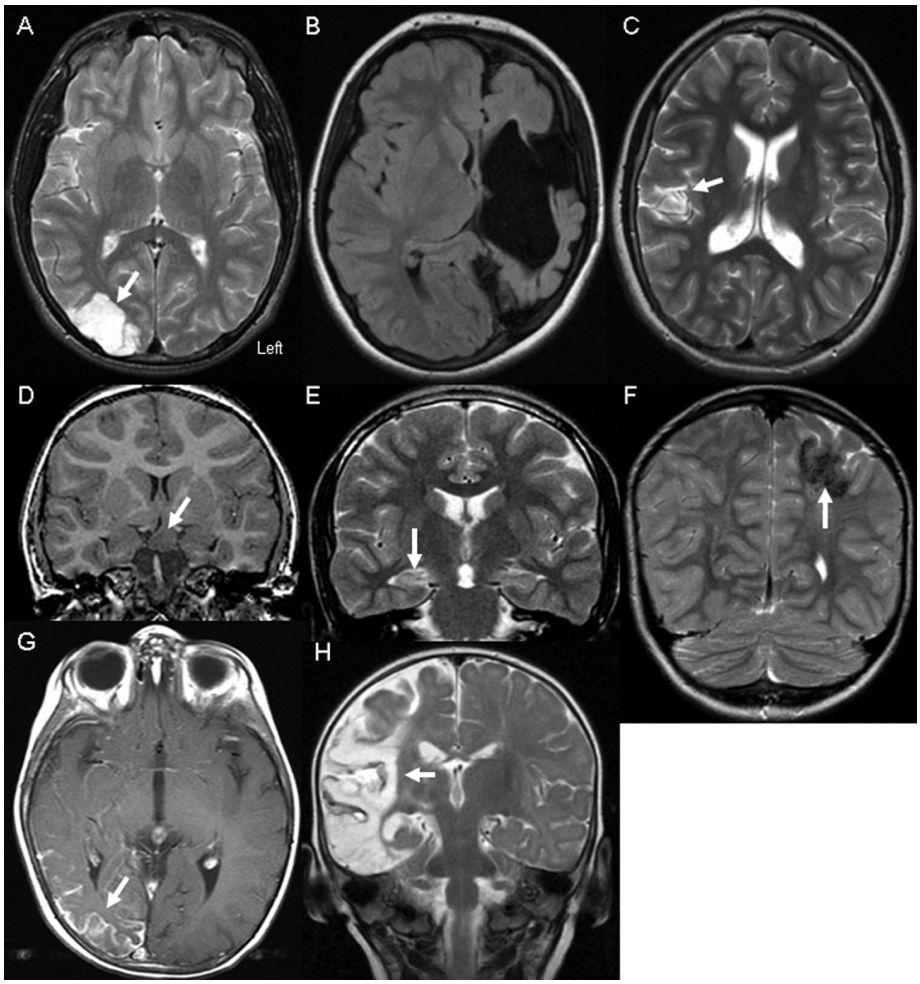

Fig. 77.2 MR scans of other aetiologies found in paediatric epilepsy surgery patients. (A) Example of a right occipital cystic mass that by histopathology was a tumour (DNET). (B) Example of a patient with a large left middle cerebral artery infarct in the perinatal period. Notice the smaller cranial vault over the left hemisphere. (C) This patient had continuous movements of the left face and hand consistent with epilepsia partialis continua (EPC) associated with an area of atrophy in the right perisylvian region (arrow). A previous MR scan 1 year before was normal. Histopathology showed findings consistent with Rasmussen encephalitis. (D) A child with gelastic epilepsy from a hypothalamic hamartoma (arrow). (E) This child had a complex febrile convulsion at the age of 18 months. From the age of 5 years the child experienced episodes of staring and lip smacking associated with an aura of a 'funny feeling in my tummy'. MRI shows increased T2 signal in the right hippocampus (arrow), which, at histopathology, was hippocampal sclerosis. (F) Example of a calcified cortical tuber (arrow) in a child with tuberous sclerosis complex. (G) This child had a port wine stain over the right eyelid. The MRI with contrast shows imaging features of Sturge–Weber syndrome. (H) This child had herpes encephalitis and later developed seizures coming from the damaged right hemisphere (arrow).

Neurocutaneous disorders (phakomatoses), such as Sturge–Weber syndrome (Fig. 77.2G) and tuberous sclerosis complex (Fig. 77–2F), are rarer causes of epilepsy in children but can be treated surgically. In patients with tuberous sclerosis, seizures may appear to be multifocal in origin, are often resistant to antiepileptic drugs and have a negative impact on the neurocognitive development [25]. Many times resection of a single tuber is necessary for optimal seizure control. In other cases, a multistaged approach with resection of multiple epileptogenic tubers may be necessary [26]. In Sturge–Weber syndrome, developmental delay and progressive hemiparesis may occur with suboptimal seizure control, and thus children may require early focal or hemispheric resection [27].

More unusual pathologies encountered in patients undergoing paediatric epilepsy surgery include Rasmussen's syndrome (Fig. 77.2C), hypothalamic hamartoma (Fig. 77.2D), polymicrogyria, Landau–Kleffner syndrome and hemimegalencephaly (Fig. 77.1B). Hemimegalencephaly is a poorly understood phenomenon in which one hemisphere is hypertrophied and contains an abnormal proliferation of unusual glial and neuronal cells, whereas the other hemisphere is smaller than normal [28]. Children with hemimegalencephaly typically have mental retardation and contralateral paresis. Abnormalities detected by electroencephalography may be unilateral or bilateral, often with hypsarrhythmia. Hemispherectomy provides the best chances for seizure control and normalization of psychomotor development velocity in children with hemimegalencephaly.

Pre-evaluation in paediatric epilepsy surgery

Evaluation of children by individuals with expertise in refractory paediatric epilepsy syndromes ensures confirmation of an accurate diagnosis and consideration of appropriate medical and surgical therapies. Not all patients referred to a paediatric epilepsy centre will be offered surgical treatment. In fact, surgery is typically withheld in patients with degenerative and metabolic disorders, benign idiopathic focal epilepsies and medication noncompliance. Many of the symptomatic pathologies are uncommon and it is to the benefit of the child to be evaluated by specialists who are experienced in diagnosing and treating rarer disorders, such as tuberous sclerosis complex, Rasmussen's syndrome and hemimegalencephaly.

Preoperative evaluation involves electroencephalography, structural and functional neuroimaging and, when appropriate, neuropsychological testing and psychiatric assessments. Interictal electroencephalography and video electroencephalography

(VEEG) telemetry are integral to localizing the seizure source and accurately recording the semiology. In certain situations, invasive electroencephalography recordings (grid or depth electrodes) may be necessary when non-invasive alternatives are inconclusive. The use of intracranial electrodes varies widely from centre to centre. Intracranial electrodes are used in approximately 25–30% of paediatric epilepsy surgery cases [21]. Structural imaging refers to MRI with specific epilepsy protocols. Sequences obtained may include T2 fast spin echo (FSE), T2 gradient echo (GE), T1 inversion recovery (IR), fluid attenuation inversion recovery (FLAIR), three-dimensional thinly sliced T1-weighted GE in three planes, magnetization transfer (MT), spoiled gradient recalled (SPGR) and diffusion-weighted imaging (DWI). Fractional anisotropy and diffusion tensor imaging are emerging MRI methods and these are used to identify structural abnormalities that could be generating seizures and to view normal white matter tract anatomy for operative planning. Of importance is the fact that immature myelination in infants of less than 24 months of age may require specialized MR sequences and serial MRI. An initial scan that is normal can become positive, showing an epileptogenic lesion with further maturation of the brain. Functional imaging consists of ictal and interictal SPECT, FDG-PET, MEG/magnetic source imaging (MSI) and blood oxygen level-dependent functional MRI (BOLD-fMRI) for mapping motor, sensory and language areas [29]. In older children, fMRI is particularly useful for identifying eloquent cortex that may affect surgical planning. The use of fMRI helps to spare normally functioning areas, identify abnormal areas that are functionally active and demonstrate areas of eloquent cortex that have reorganized [30]. In about 50% of paediatric epilepsy centres, intracarotid amobarbital infusion is used for language lateralization [21]. At most paediatric centres, multimodal integration of imaging data is performed routinely, with MEG and PET data superimposed on to structural MRI acquisition data in order to assist surgical planning.

Because many paediatric epilepsy disorders are also associated with psychiatric and cognitive co-morbidities, evaluation by an interdisciplinary team of developmental neuropsychologists, psychiatrists and social workers is an important step in the pre- and postsurgical processes. This includes appropriate assessment of family dynamics regarding the expectations for surgery. The process of deciding if surgery is the most appropriate therapeutic intervention depends on an analysis of the intervention's risk–benefit ratio compared with the risks of continued uncontrolled epilepsy. Clinicians and families must decide together whether the risk of continued seizures justifies the risks of epilepsy surgery, including any expected postoperative physical and neurological deficits.

The evaluation and surgical treatment of paediatric epilepsy are customized to the individual child. For example, it is not uncommon for children with symptomatic substrates to present with acute status epilepticus that requires urgent surgery to control life-threatening seizures [31]. Surgery may be directed to invasively record seizures using grid and depth electrodes, resect the epileptogenic lesion, disconnect the abnormal cortex using different techniques or palliate seizure frequency [21]. Approximately 80% of seizure surgery in children involves resection and invasive diagnostic electoencephalography procedures, whereas 20% involves palliation. The most common types of surgery are shown in Table 77.2. About 15% of patients receive hemispherectomy, 13% multilobar resections, 58% localized resections and less than 5% receive only diagnostic electrophysiological recording or multiple subpial transections (MSTs). Multiple techniques of hemispherectomy–hemispherotomy exist, all with relatively similar seizure control rates and efficacy similar to temporal lobectomy for complex partial limbic seizures [9,32,33]. At our institution we use a modified lateral hemispherotomy, which, when compared with other methods of hemispherectomy, results in lower intraoperative blood loss, reduced complication rates and shorter intensive care unit stays [10,17]. In children who receive localized or multilobar resections, seizure control is directly related to the completeness of lesion excision. Multiple subpial transections are useful for children with epileptic lesions in eloquent cortex, in whom transverse synaptic connections can be disrupted while preserving functional vertical columns.

Table 77.2 Frequency of types of paediatric epilepsy surgery in children under the age of 18 years.

Location	Cases (%)
Temporal	30
Frontal	23
Hemispherectomy	20
Multilobar resection	18
Parietal	3
Hypothalamic	3
Occipital	2
Multiple subpial transection/no resection	1

Modified from ref. 21.

Of children who qualify for palliative procedures, most receive vagal nerve stimulators in the USA, whereas only a few receive corpus callosotomy. Corpus callosotomy is a more frequent operation in parts of the world without access to vagal nerve stimulators. These procedures are typically performed in children with catastrophic generalized epilepsy not amenable to resection, such as seen in Lennox–Gastaut syndrome [34]. Radiosurgery has recently emerged as a surgical alternative, particularly in those with hypothalamic hamartoma and mesial temporal lobe epilepsy in older children and adults. The use of radiosurgery in infants and small children has not been adequately studied. Stereoendoscopic techniques have also emerged as new approaches to the treatment of epilepsy in children with hypothalamic hamartoma [35,36].

The appropriate anaesthesia team is necessary in children undergoing epilepsy neurosurgery [37]. Infants have lower cerebrovascular autoregulatory reserves and a relatively high cerebral blood volume, putting them at greater haemodynamic risk during extensive neurosurgical resections. The head constitutes approximately 20% of the body surface area in infants and children, compared with 9% in an adult. Also, infants have a limited capacity to handle changes in fluid and solute loads, affecting fluid management during surgery. Hepatic function can be considerably altered in children on chronic antiepileptic drug (AED)

therapy, and thus drug metabolism and coagulation may be affected. These issues are of importance when considering epilepsy surgery on small children, as high intraoperative blood loss and transfusion requirements (especially in the case of large resections, e.g. anatomical hemispherectomy) may cause considerable haemodynamic and metabolic derangements. A unique example where this is especially poignant is hemimegalencephaly, when the immature, dysplastic hemisphere is particularly vascular and blood transfusion requirements may be considerable. Although haemodynamic risks may at initial glance make one wary of operating on young children when larger resections are usually necessary, the increased operative risks are justified in order to prevent cognitive and developmental delay due to longstanding epilepsy during early brain development.

Preoperative anaesthesia evaluation should include haematological and metabolic analyses, as well as chest radiography and, possibly, echocardiography. In the case of children with tuberous sclerosis complex, appropriate imaging should be performed to rule out lesions in other organ systems that may affect intraoperative physiology, such as the heart and kidneys. An accurate medication history is essential, as many AEDs affect the metabolism of anaesthetic agents. Furthermore, the use of the ketogenic diet may promote metabolic derangements when carbohydrates are administered, and therefore only normal saline should be utilized. Intraoperative monitoring should focus on continuous haemodynamic assessment, and placement of an arterial line and central venous access are necessary. Postoperative care in the paediatric intensive care unit should focus on maintenance of appropriate haematological and coagulation parameters. Surgical drains are utilized many times, especially in the case of larger resections, and intracranial pressure management is important. An experienced multidisciplinary team, consisting of neuroanaesthesiologists, paediatric intensivists, paediatric neurologists and the neurosurgeon, should guide perioperative and postoperative management.

Outcomes in paediatric epilepsy surgery: seizure remission and cognitive/psychosocial results

In a recent study examining 134 children who underwent epilepsy neurosurgery, the overall seizure-free rate was 69% over a mean follow-up time of 62.3 months [38]. This is consistent with other studies that have reported that 65–80% of children become seizure free after epilepsy neurosurgery [9,32]. The seizure-free rate is higher in children who have temporal resections for discrete MRI-identified lesions than extratemporal resections for MRI-negative or ill-defined lesions without clear borders [39]. Early seizure control after epilepsy surgery is the best predictor of long-term control. Patients who do not have a seizure recurrence during the first 6 postoperative months have up to a 95% chance of being completely seizure free over the long term [40]. Successful control of seizures after epilepsy surgery in children is associated with reduced use of AEDs [33,41]. Approximately 30–50% of children discontinue use of AEDs after epilepsy surgery. Seizure freedom after surgery is associated with lower mortality [33].

In studies of focal resection for localized epilepsy, seizure-free rates have been shown to be up to 88% for hippocampal sclerosis, 50% for dual pathology, 81% for tumour, 62% for cortical dysplasia and 80% for cavernous malformations [42]. These focal resections have only rarely been associated with permanent neurological complications. The reduction in seizures is greater in patients with pathologies requiring focal or lobar resections than in patients with a more widespread and diffuse pathology requiring multilobar surgery [43]. That being said, epilepsy surgery may be successful for selected children and adolescents who present with abundant generalized or bilateral epileptiform discharges on electroencephalogram (EEG). Diffuse EEG patterns may indicate an interaction between the lesion and the developing brain [44]. Failure of surgical treatment is related to the absence of radiographic evidence of a structural abnormality, development-associated disease, widespread disease on postoperative EEG, and limited resection due to involvement of functional cortex. Presurgical intellectual disabilities do not predict postoperative seizure outcomes in paediatric epilepsy surgery patients [45].

Risks and complications of epilepsy neurosurgery are reasonably low when compared with the cognitive, developmental and mortality risks of chronic suboptimal seizure control. Surgical mortality is less than 1% for temporal lobectomy and 1–2% for hemispherectomy. Permanent morbidity from surgical resection is generally reported to be less than 5%, with risks varying by type of procedure performed. Temporal resections are most often complicated by visual field deficits, while extratemporal resections are most often complicated by transient hemiparesis [32]. Serious complications include infarct and hemiparesis in temporal lobe resections and motor or language deficits in larger procedures. Operative morbidity and mortality rates are less than those of uncontrolled therapy-resistant epilepsy.

The literature supports the notion that after epilepsy surgery, developmental quotients improve when seizures are controlled. Developmental indices before surgery predict postoperative developmental function [16,40]. Children operated on at younger ages and with epileptic spasms show the greatest increase in developmental quotient after surgery. Studies have also shown a mean increase in IQ following surgery, particularly in patients with a shorter seizure history [46]. Specific cognitive functions, such as behaviour and attention, typically impaired in parietal lobe epilepsy, are improved by epilepsy surgery as well [45]. This translates into better school performance and social adaptation after paediatric epilepsy neurosurgery. Memory and executive function do not seem to be adversely affected by epilepsy surgery in children. Furthermore, epilepsy surgery does not appear to adversely affect motor performance with regards to daily activities and level of caregiver assistance [47]. Although more longitudinal studies are needed to adequately assess cognitive and neurodevelopmental results in epilepsy surgery patients, preliminary data indicate that these faculties are improved.

Studies show that quality of life (QOL) is enhanced after epilepsy neurosurgery in children. Most improvements in QOL occur in the first 6 months after surgery. One study found that all patients who underwent epilepsy surgery experienced improvement in QOL measures, with seizure control being clearly correlated with QOL changes [48]. Children, after epilepsy surgery, experience greater feelings of self-worth and social competence.

Similarly, after surgery, adolescents feel better about their athletic competence and capacity for social interactions. This improvement in QOL is critical for social integration of these children among their peers. In addition, in children who undergo temporal lobectomy QOL indices normalize to that of matched healthy individuals 3 years after surgery [49]. In contrast, intractable temporal lobe epilepsy without surgical therapy has been associated with low QOL scores despite attempts at AED optimization. Studies have also indicated that epilepsy surgery is cost-effective, especially for children, and allows other members of the family to engage in work and school.

Conclusion

Children with therapy-resistant epilepsy are at particular risk for developmental delay, cognitive regression and higher mortality rates. Early identification of intractability and referral to a paediatric epilepsy centre is crucial. Children with structural lesions visible on MRI and who have failed to respond to two to four AEDs have a poor chance of being seizure free on medications and should be quickly referred to a specialty centre for evaluation because of increased seizure-related morbidity and mortality. If the child is a candidate for surgery, preoperative studies include interictal electroencephalography, VEEG telemetry, structural and functional neuroimaging and, when appropriate, psychiatric and cognitive evaluations. Surgical intervention for these children is directed at reducing seizure frequency while minimizing neurological morbidity. Overall seizure control rates are from 65% to 80% after epilepsy neurosurgery in children. Morbidity and mortality rates are reported as less than 5%, which compare favourably with the higher mortality of therapy-resistant epilepsy over 10 years. Furthermore, recent studies have shown that epilepsy surgery improves developmental and cognitive indices and QOL. Thus, surgery for intractable epilepsy in children should not be the treatment of last resort. Instead, it should be considered along with medical treatment to stop seizures as soon as possible to prevent epilepsy-induced disabilities in infants and children.

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78 Stereotactic Surgery for Epilepsy

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Introduction

The evolution of surgical treatment for epilepsy in the last century has been critically dependent on technical development [1]. Conventional (i.e. resective) surgery for medically refractory epilepsy has a long tradition and is effective in cessation or amelioration of seizures in 55–80% of patients depending on case selection. Stereotaxy is a navigational technology that allows neurosurgeons to accurately determine their location and direction during surgery. Stereotactic procedures offer the possibility of being highly accurate, more economical and better tolerated than conventional craniotomy and resective surgery; hence these are being used more frequently in the management of medically refractory epilepsy.

During the past decade, technological advances have revolutionized the art of neurosurgical navigation, with frameless stereotaxy perhaps the most elegant. More recently, there has been a trend towards using stereotactic radiosurgery with the gamma knife for placing highly selective discrete lesions in areas of the brain responsible for epilepsy.

The word 'stereotactic', derived from the Greek *stereos* (meaning 'three-dimensional') and *tactus* (meaning 'to touch'), was coined by Horsley and Clark in 1906 [2]. The technique involves the use of neuroradiological imaging modalities, linked to a three-dimensional coordinate system, in order to guide the surgeon to a chosen target with an accuracy of 1–2 mm.

Traditionally, registration of the radiological images to the patient in the operating theatre has involved the use of a stereotactic head frame. This is fixed to the patient's head with screws, is visible on the imaging modality being used and remains on the patient's head during surgery. This rigid head frame has the major advantage of maintaining a fixed three-dimensional coordinate system. Unfortunately, however, the bulky frame is also the system's main limitation, as it puts a constraint on head positioning and physically interferes with performing a craniotomy. Consequently, frame-based systems tend now to be reserved for procedures such as needle biopsy or placement of depth electrodes.

The next step was the development of image-based, intracranial navigation that is independent of an external frame. Several systems have now been developed, each based on a combination of three fundamental concepts: (1) correlating physical space with image space; (2) using a pointing device for interactive localization; and (3) obtaining image-guided feedback through a computer-based interface. Frameless stereotaxy is based on the creation of a mathematical relationship between radiographic images and physical space. This process, known as registration, involves the precise mapping of every location in an image to the corresponding physical anatomy of the patient [3].

The application of stereotactic neurosurgery continues to advance, especially with developments in multimodality neuroradiological imaging. The advent of high-resolution (3-T) MRI, MR sequences demonstrating previously unseen focal lesions and diffusion tensor imaging (DTI), together with functional imaging modalities such as functional MRI (fMRI), magnetoencephalography (MEG), positron emission tomography (PET), singlephoton emission computerized tomography (SPECT) and electroencephalography–fMRI, allied with advances in computer and stereotactic instrument technology, has introduced new possibilities in epilepsy treatment.

The use of preoperative high-resolution volumetric MRI has had an enormous impact on epilepsy surgery planning [4–9]. The responsible pathological substrate is now frequently identifiable using such methodologies [10,11]. In the epilepsy surgery programme at the National Hospital for Neurology and Neurosurgery, London, UK, the number of such abnormalities visualized on preoperative imaging of epilepsy surgery candidates has risen from less that 10% to over 90% with the routine use of volumetric MRI. In this way, epilepsy surgery is becoming increasingly image guided, with less reliance placed on electrophysiological localization. Frameless stereotactic neurosurgery is frequently the method by which this image guidance is best achieved.

In this chapter, we will discuss the principles of stereotaxy and their application to the basics of 'frame-based' and 'frameless' systems. We will show how the increasing use of multimodality imaging and its integration into image-directed neuronavigational systems has led to these techniques becoming an essential part of epilepsy surgical practice.

We will discuss the current status of stereotactic neurosurgery in the surgical management of epilepsy with reference to its role:

- As an aid to conventional (i.e. resective) epilepsy surgery:
  - *Diagnosis*. Stereotactic methods are used to place depth electrodes for invasive electroencephalographical monitoring in the evaluation of epilepsy cases in which there are diagnostic and management difficulties concerning lateralization and localization.
  - *Treatment*. First, selective stereotactic amygdalohippocampectomy has been used as a method of minimizing the

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resection of the lateral temporal neocortex while continuing the resection to the relevant part of the mesial temporal structures in patients with temporal lobe epilepsy in whom there is concern over the neuropsychological status (particularly with regard to postoperative memory function). Second, stereotactic neurosurgery can be used to guide the surgeon towards small epileptogenic lesions using the techniques of image directed craniotomy.

- For stereotactic lesion making in the central nervous system (i.e. non-resective surgery).

However, it must be appreciated that image-directed surgery is now an inherent part of neurosurgical practice. Its use has become widespread and it is easily applied to almost all neurosurgical procedures.

Frame-based stereotactic neurosurgery

Traditional frame-based stereotaxy offers a high degree of point target localization, but unfortunately the identical stereotactic space is not easily reproducible in the individual patient on different occasions (Plate 78.1). Furthermore, skull fixation using either screws or pins is invasive and uncomfortable for the patient. As a result, with traditional head frames the two phases of stereotaxy (i.e. image acquisition and surgery) need to be closely related to one another in time – in general, one following directly after the other [12,13]. Frameless stereotactic methodologies offer the potential for comprehensive image guidance not seen with frame-based stereotaxy.

Frameless stereotactic neurosurgery

Frameless stereotaxy is uniquely suited to intracranial surgery. The relatively fixed position of the brain within the skull facilitates the referencing of preoperative data with the real-time position of the head.

The main advantages of frameless stereotaxy are that it provides real-time, updated information to the surgeon regarding location and trajectory. It can be helpful in localizing lesions, increasing the chances of complete lesion resection and helping to identify normal structures surrounding a lesion. Typically, the result is faster, more complete and often safer neurosurgical procedures.

Frameless stereotaxy is invaluable at all stages of image-directed epilepsy surgery, including selection of the preoperative approach, sizing of the scalp incision, placement of the craniotomy and selection of the trajectory through or around cerebral structures. Resection of tumours is improved, with corticotomies precisely placed. In tumours with poorly defined margins, the constant feedback on location can be invaluable in maximizing tumour resection while minimizing brain injury. With frameless stereotactic neurosurgery, the surgeon can be accurately and easily guided to the area(s) in the brain responsible for the epilepsy [3].

There are four components to a frameless stereotactic neurosurgical system:

1 pointing device (e.g. a wand);
2 tracking system, which is constantly locating the position of the localizing device in space;
3 hardware system represented by a central processing unit (CPU) and an output device (monitor);
4 software, which is able to reconstruct the data from the tracking system into a three-dimensional image, and is able to register the preoperative image dataset on physical space [14].

Image space is the three-dimensional volume represented by the series of multimodality neuroradiological images that are acquired preoperatively and which make up the imaged anatomy of the patient. Anatomical images obtained from CT and MR scans are frequently defined in the image space and are of high resolution; images from other functional imaging modalities (fMRI, PET and SPECT) can be integrated and also used in image space [15]. As each point in either the CT or MR image dataset is defined in terms of a three-dimensional coordinate (x, y and z), relative to the origin of the Cartesian frame of reference [16], and as each coordinate has an intensity value, these imaging modalities have an already established three-dimensional coordinate system that relates each point in the image to the anatomy. Physical space is the three-dimensional volume represented by the real physical anatomy of the patient and, as such, does not have an obvious coordinate system.

Frameless stereotaxy aims to define a three-dimensional coordinate system for the physical space, and superimpose the images of the anatomy of the patient from the CT or MRI data (i.e. the image space) on to the actual anatomy of the patient in the operating theatre (i.e. the physical space), and thus create a real-time navigational map that the surgeon will use throughout the surgical procedure. This process is called *registration*.

One of the earliest technologies used to localize a point in space consisted of an articulated arm [17–24]. The ISG viewing wand frameless stereotactic guidance system (ISG Technologies, Mississauga, Ontario, Canada) is an excellent example and was used extensively in neurosurgery because of its accuracy to less than 2 mm (Plate 78.1c and d). The wand consists of two segments: a sterile surgical probe and a multijointed, articulated arm with six joints, which gives it a 60-cm reach and six degrees of freedom. Electrical signals from the joints are relayed to and processed by the CPU to give an accurate location of the probe tip in physical space.

The more recent technologies use a system to localize a point in physical space using less bulky and obstructive pointing devices (Fig. 78.1). These systems use a 'free-hand' pointing tool. The data acquisition methods of these free-hand pointing tools are similar. Essentially, the free-hand pointing tool is capable of sending data to a receiver (a microphone or a camera), which will send the received signals to the main CPU without there being a direct physical connection between the tool and the CPU. The CPU will then be able to compute the precise location and three-dimensional coordinates for the pointing tool.

The first examples of these used an ultrasonic triangulating system [25,26]. The more recent systems rely upon the pointing device emitting infrared light from emitting diodes (iLEDs) to cameras located around the operating theatre [27,28]. This information is then processed by the CPU, in the similar way to the ultrasound triangulating system. Although the path between the iLEDs and the camera must be clear, this system does not suffer the disadvantage of interference or of temperature changes. The accuracy of the pointing device is continually assessed during the surgical procedure with known anatomical landmarks. These systems have the advantage that almost any surgical instrument can be converted to the pointing device.

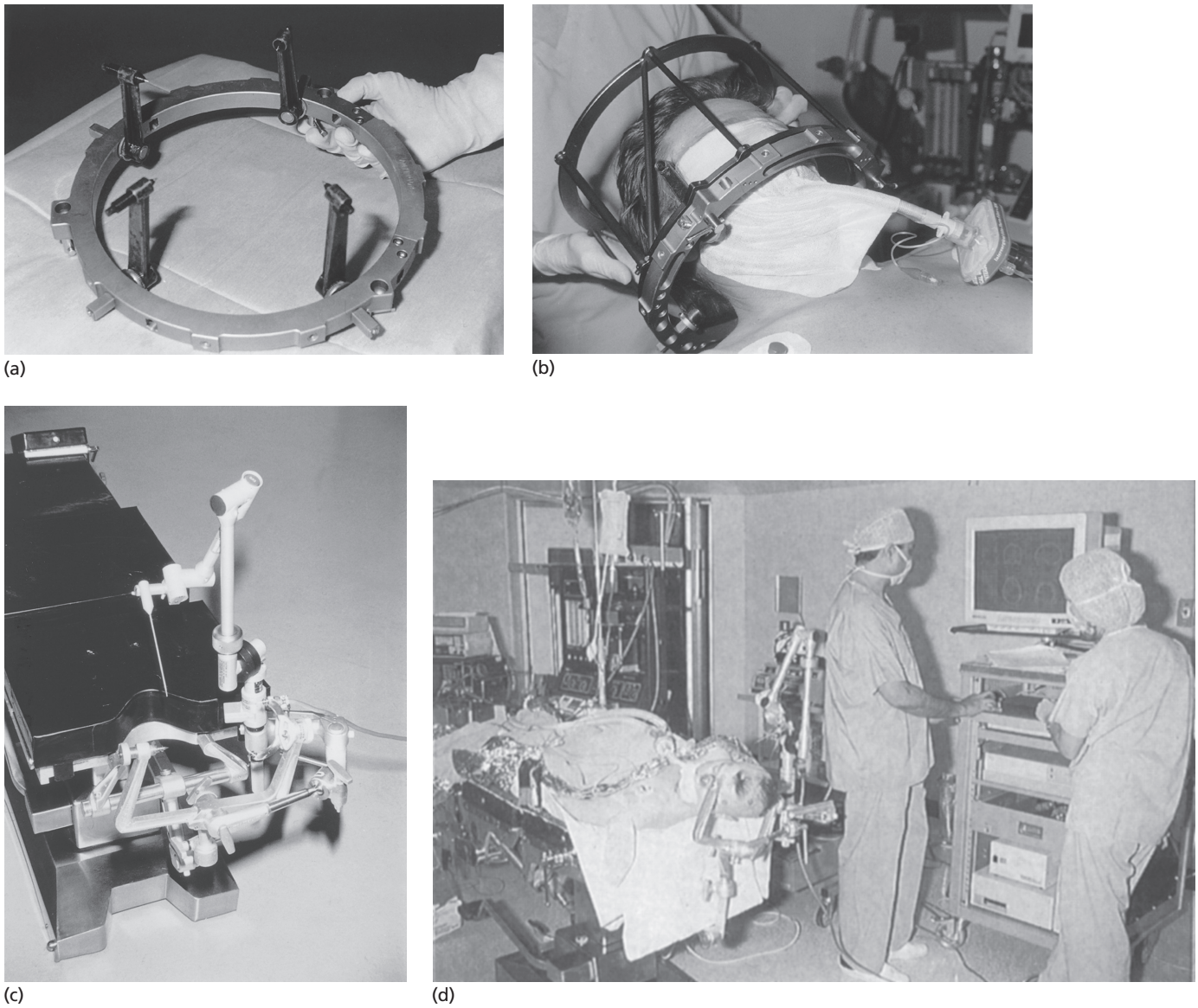


Fig. 78.1 (a) The Cosman–Roberts–Wells base ring. (b) The Cosman–Roberts–Wells base ring and fiducial system being used introperatively. (c,d) The ISG 'Viewing wand' uses a passive mechanical arm for registration and pointing during surgery.

A further development incorporates the localizing function into the operating microscope. Several systems have been developed, one example being the Leica Viewscope (Leica, Deerfield, IL, USA), in which the pointing function is performed by two low-energy lasers that are designed to converge at a single point at the focal length of the microscope. After mapping this point to image space, the corresponding location on the imaging studies can be visualized. These systems have the advantage of continuous update, without the need for a separate pointing device. Although most systems require the surgeon to look away temporarily from the operating field to the computer display, some newer systems incorporate heads-up display of the frameless stereotactic data.

Another recent advancement is the development of frameless stereotaxy without rigid pin fixation. The accuracy and precision of resection with awake brain mapping is greatly augmented when combined with stereotaxy, as described below. Frameless stereotactic-assisted surgery, however, typically involves immobilization in Mayfield pins, which can be uncomfortable for patients undergoing awake craniotomy and can cause complications in paediatric cases. We have recently started to use the Medtronic Stealthstation® Axiem™ system in our institution, which enables similar accuracy of frameless stereotaxy [29] without the requirement for immobilization in Mayfield pins (Plate 78.2). In the future, we also anticipate that the use of intraoperative MRI will be considerably facilitated by frameless stereotaxy without rigid pin fixation.

Registration of the image space on to the physical space is required for the navigational map to be produced. The precise way in which this is achieved is beyond the scope of this chapter; however, there are two basic systems – pairedpoint registration and surface registration.

Paired point registration uses natural landmarks, for example external auditory meatus, nasion or lateral canthus [20,28,30,31],

or artificial landmarks (fiducial markers placed on the head) that are visible on CT and MRI scans [22,25–27,32,33]. Registration error is theoretically minimized at the epicentre of the registered points, so fiducials should be placed on the scalp so they 'surround' the lesion. The most precise landmarks for registration are either bolts or screws in the skull [31].

Surface-based registration systems match numerous points extracted from natural contours. They attempt to align the contour of a physical surface (such as the scalp) with a corresponding image surface.

The corresponding landmarks on the physical space are identified on the image space. With both datasets stored in the CPU, a 'best-fit' transformation matrix is applied by the CPU, transforming and superimposing image space on to physical space as accurately as possible. Hence, the surgeon can readily determine location and trajectory throughout the surgical procedure and the result is navigation.

The disadvantages of image-directed guidance systems are the learning time required to become fully confident with using the device, the preoperative set-up time and the space required for the system in the operating theatre [19]. In addition, changes in the cerebral blood volume, mechanical ventilation, cerebrospinal fluid withdrawal, unopposed gravity and patient positioning can all affect registration. Other problems are brain shift once the skull has been opened or a mass lesion is removed. In this case, the preoperative images will no longer provide an accurate picture of the anatomy of the contents inside the skull. The most definitive solution to this problem is the use of intraoperative MRI and frameless stereotaxy [34–49]. The neurosurgeon can then periodically update the reference images and re-register physical space to updated image space in 'real time'. In other words, the images directing the surgery are not 'historical', but rather are providing information about what is actually occurring during the surgical procedure. The effects of brain shift, which can lead to inaccurate neuronavigation, can therefore be compensated for by an update of the neuronavigation system with intraoperative MR image data. In addition, intraoperative MRI allows resection control images with precise localization of residual tumour tissue and may improve complication avoidance. It also enables online image-guided stereotaxy without preoperative imaging, and 'real-time' tracking of instruments in the operative field. Currently, the main indications for intraoperative MRI are the evaluation of the extent of a resection in glioma, ventricular tumour, pituitary tumour and in epilepsy surgery. Intraoperative MRI offers the possibility of further tumour removal during the same surgical procedure in case of tumour remnants, increasing the rate of complete tumour removal. Claus *et al.* [50] have demonstrated a possible association between surgical resection and survival for neurosurgical patients who underwent surgery for low-grade glioma under intraoperative MRI guidance, and suggested that further study within the context of a large, prospective, population-based project will be needed to confirm these findings. Wirtz *et al.* [51] and Wu *et al.* [52] have demonstrated that the more extensive removal of glioblastoma multiforme enabled by intraoperative MRI leads to significantly prolonged patient survival compared with conventional surgery, but further research is required to determine whether this technique may increase survival in those with low-grade tumors. Another technique of upgrading the accuracy of the navigation system intraoperatively is with ultrasoundd [53–57], which has been shown to be a useful adjunct for the resection of arteriovenous malformations [54] and metastases [55].

Multimodality imaging and image-directed neurosurgery

The last decade has seen neuroimaging take an increasingly important role in the management of epilepsy. New techniques and imaging sequences have appeared that give ever greater sensitivity in the search for abnormalities of brain structure. Neuroimaging has become a powerful functional tool of high spatial resolution that has increased in temporal resolution to the point where it has become an important physiological probe of functions that were previously considered to be entirely the domain of electrophysiology.

A number of imaging modalities are now in common use for the localization of seizure foci as part of the preoperative investigation of patients with intractable epilepsy. In addition, non-invasive methods of mapping brain function, such as functional MRI (fMRI) [58–64], magnetoencephalography (MEG) [65–69], and poistron emission tomography (PET) with the tracer $[^{15}O]H_2O$ are playing an increasing role in the presurgical planning and in intraoperative surgical guidance [15,70–73] (Plate 78.3). However, although these various diagnostic methods can be useful in the diagnosis of epileptic foci, and concordance between presurgical evaluations indicates a better surgical outcome, MRI at present best predicts surgical outcome [74]. MEG can also been used to complement electroencephalography in patients with normal or non-focal MRI findings to determine surgical targets [75]. Also, in patients who are treated surgically for temporal lobe epilepsy the use of these techniques has potential in minimizing morbidity by accurately defining areas of brain function that may be altered, such as language lateralization [76–80].

An exciting new prospect is to combine different types of imaging with complementary information. This has two main uses in epilepsy surgery: first, to minimize surgical morbidity by accurately defining areas of brain function, such as the combination of fMRI and tractography described later; and, second, to enable more precise localization of the epileptic source, such as EEG-correlated functional MRI (EEG-fMRI) [81–85]. Simultaneous acquisition of electroencephalography and fMRI data enables the investigation of the haemodynamic correlates of interictal epileptiform discharges (IEDs) during the resting state in patients with epilepsy. fMRI activation can localize the irritative zone and indicate functional disturbance distant from the spike focus. Salek-Haddadi *et al.* [84] investigated the blood oxygen level-dependent (BOLD) signal correlates of IEDs in 63 consecutively recruited patients with focal epilepsy. Significant haemodynamic correlates were detectable in 68% of patients in whom discharges were captured, and were highly concordant with site(s) of presumed seizure generation where known. Focal activations were more likely when there was good electroclinical localization, frequent stereotyped spikes, less head motion and less background electroencephalography abnormality, but were also seen in patients in whom the electroclinical focus localization was

uncertain. They concluded that EEG-fMRI may provide new targets for invasive electroencephalography monitoring. Lengler *et al*. [82] used EEG-fMRI to study 10 children with typical and atypical benign focal epilepsy of childhood or benign epileptic activity of childhood, and also concluded that it is a useful technique to localize generators of IED. Zijlmans *et al*. [83] have demonstrated the potential added value of EEG-fMRI in the presurgical evaluation of patients with complex source localization. Adult surgical candidates considered ineligible because of an unclear focus and/or presumed multifocality using EEG underwent EEG-fMRI. IEDs in the EEG during fMRI were identified by consensus between two observers. In total, 29 patients with significant, positive BOLD responses that were topographically related to the electroencephalography were re-evaluated for surgery; eight patients were rejected for surgery because of an unclear focus (3), presumed multifocality (2) or both (3). EEG-fMRI improved localization in four out of six unclear foci. In five patients with presumed multifocality, EEG-fMRI revealed one focus in one patient and confirmed multifocality in four patients. In four patients EEG-fMRI opened new prospects for surgery, and in two of these intracranial electroencephalography supported the EEG-fMRI results. In these complex cases, EEG-fMRI either improved source localization or confirmed a negative decision regarding surgical candidacy. Liston *et al*. [81] have further refined this technique by analysis of EEG-fMRI in focal epilepsy based on automated IED classification and *signal space projection*, which reduces the subjectivity of visual IED classification and results in more objective fMRI models of IEDs, as well as increasing experimental fMRI efficiency by significantly increased sensitivity of IED detection. A further recent development is the combination of EEG-fMRI with tractography to delineate the pathways of propagation of epileptic activity [85], which is described below.

Multimodality imaging is now used widely in image-directed surgery. CT, MRI, fMRI, MEG, PET, SPECT and EEG-fMRI contain complementary anatomical and physiological information.

Computerized tomography and MRI scans provide images of the anatomy of the patient. These have good spatial resolution, with MRI giving the best spatial resolution. Functional brain mapping gives information on the location of the main functional areas of the cortex (somatosensory, somatomotor and language) but this imaging has lower spatial resolution. The anatomical location of the functional abnormality can be determined with greater certainty by aligning the functional images with the anatomical images.

Thus, there are two main areas in which multimodality imaging has been used in the investigation and surgical treatment of patients with intractable epilepsy: for functional mapping as an aid to surgical planning and guidance and for localization of the seizure focus.

Functional cortical mapping can have an essential role in resections in eloquent areas of the brain, to assess the surgical risks to normal cortical function and thus to plan the extent of surgical resection. The lesions that cause epilepsy often distort normal cerebral functional anatomy [1]. However, the place of functional imaging as a replacement for intraoperative electroencephalography, somatosensory evoked potentials and awake craniotomy and stimulation [86] has still to be established. In theory, functional imaging has the advantages that it can be used for preoperative planning, the patient does not need to be awake during surgery, operation time is reduced and there is no need for interactive patient cooperation during the procedure.

The integration of functional imaging information can help to accurately localize and delineate the seizure focus [58,87,88]. This offers the surgeon an extensive and more precise stereotactic navigational map that can be used to safely, accurately and optimally guide the neurosurgeon to the focus, with little or no damage to normal brain tissue.

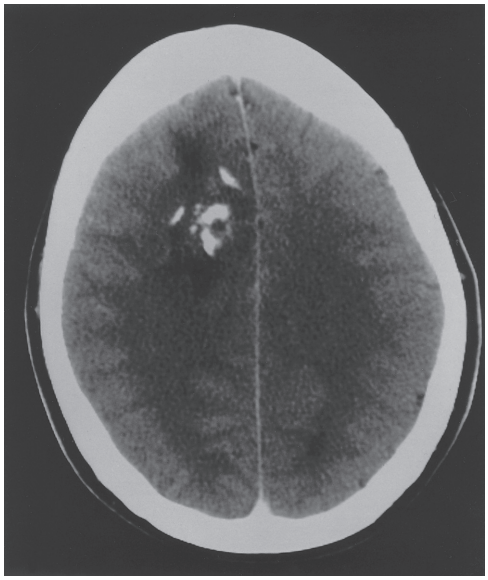
Clinical diffusion MRI (including diffusion tensor MRI and fibre tractography) is a new technique that may have great value in the imaging of epilepsy [89]. The theoretic underpinnings of this technique have recently been reviewed [90]. It allows delineation of white matter tract pathways, which enables it to delineate white matter pathways of functional importance close to an area of surgical [52,91–97] or radiosurgical [98,99] lesioning, demonstrate the alteration of white matter connections that may underlie alterations in brain function in patients with epilepsy, such as disrupted memory and language in temporal lobe epilepsy [100,101], or in the future, in combination with EEG-fMRI [85] or MEG [102], demonstrate white matter connections originating from an epileptogenic focus to delineate pathways of propagation of epileptic activity, which could be a potential target for surgical lesioning. The combination of fMRI and tractography offers a promising tool for studying the reorganization of language functions in epilepsy, and may enable predictions of language deficits following temporal lobe surgery [101,103]. The combination of mapping axonal architecture by diffusion tensor MRI fibre tracking and functional cortical neurones by intraoperative cortical stimulation can be used to delineate the pathways between functional regions. Importantly, the combined techniques also enable improved preservation of eloquent regions during surgery. For example, the combination of intraoperative tractography-integrated functional neuronavigation and cortical or subcortical stimulation in patients with brain lesions adjacent to the corticospinal tract enables accurate identification of the corticospinal tract during surgery, allowing its preservation and avoidance of tract injury while accomplishing optimal tumour resection [52,91–97].

In the future, as techniques evolve and registration improves, the incorporation of EEG-fMRI [81–85], clinical diffusion MRI [52,85,91–97,101,103], SPECT [10,104,105], PET [71], fMRI [58,87,88], MRI spectroscopy [106–109] and magnetoencephalographic data [110] into the evaluation and surgical planning of an epilepsy patient may become routine [111–114].

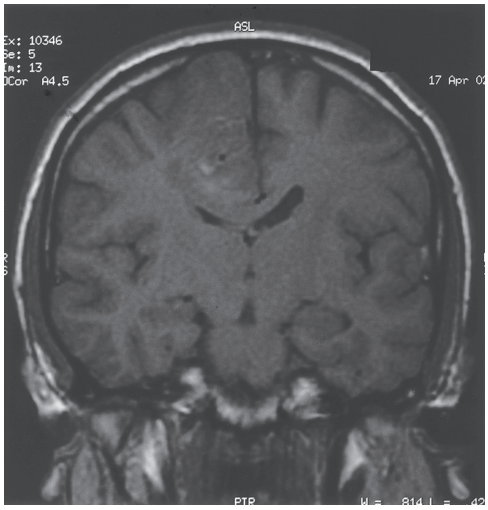
Stereotactic surgery as an aid to conventional surgery

Diagnosis: depth electrodes and stereotactic electroencephalography

The role of invasive electrophysiological monitoring using depth electrodes (and other methods such as subdural grid electrodes and epidural pegs) is diminishing [4]. These changes are due to the increasing ease with which the structural changes within the brain responsible for the epileptic phenomena can now be identified using multimodality imaging techniques.



(a)



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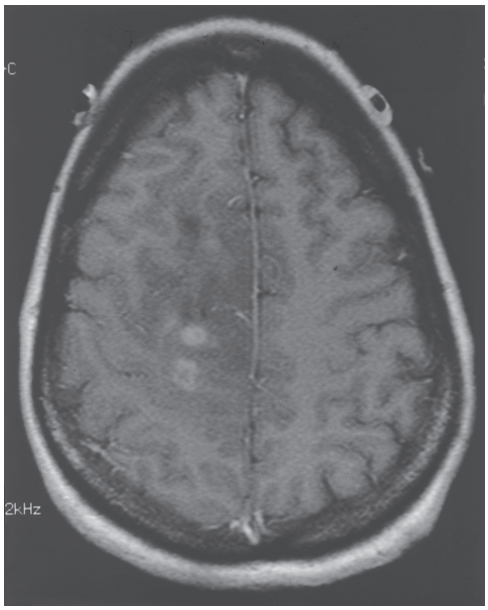

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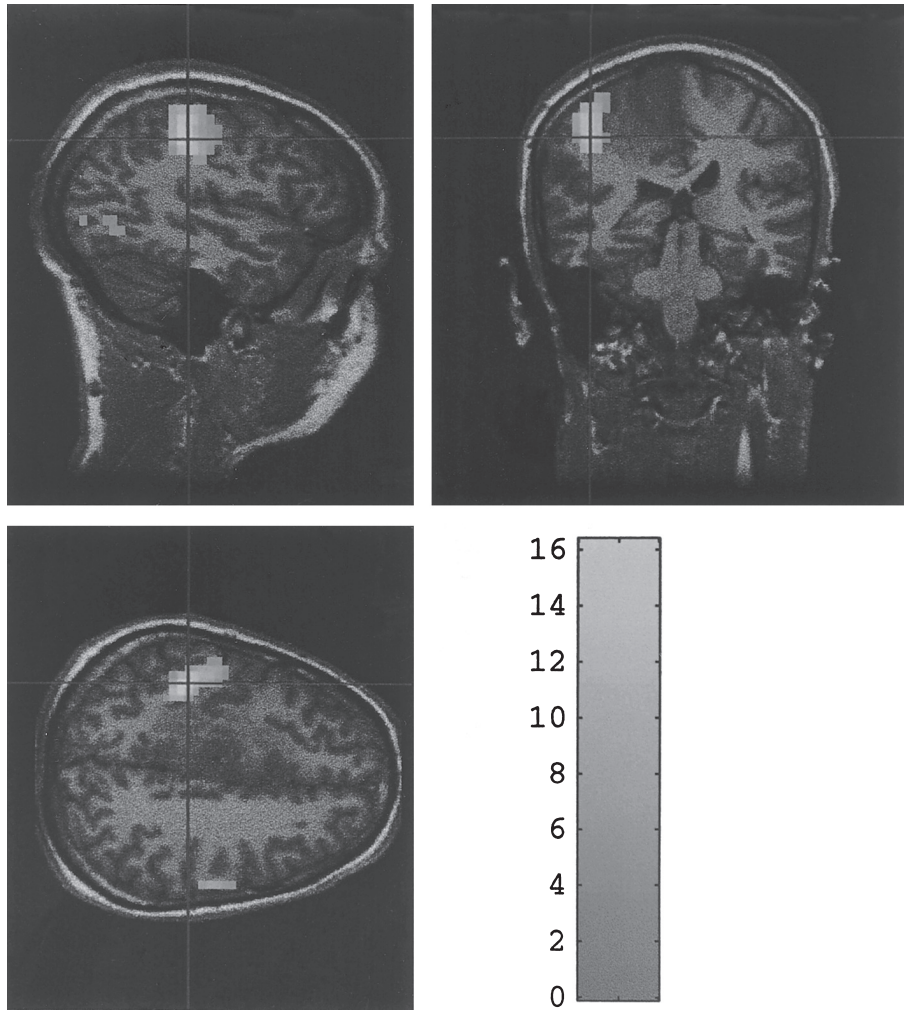

(d)

Fig. 78.2 CT (a), axial (b) and coronal (c) MRI of an epileptogenic, right-sided, calcified, posterior frontal tumour. Including functional MRI data during left-hand movement (d) in the image-guided operative data demonstrated that it was possible to resect the tumour anterior to the motor strip.

Intraparenchymal electroencephalography monitoring began with the stereoencephalographic method introduced by Talairach *et al.* [115], and has progressed through stereotactic angiography [116] and CT-guided stereotactic techniques [117–119] to multimodal stereotactic imaging using CT, MRI, PET and angiography (Fig. 78.2) [120]. As stereotactic imaging has improved, so has the safety of the procedure [121].

In 1974 Talairach *et al.* described 400 instances of 'stereoencephalographie' in 300 patients over a 14-year period; 20–30% of the patients studied were subsequently operated upon, of whom 80% had a good or worthwhile result. These authors were therefore using 'stereoencephalographie' as the routine by which to accurately localize the epileptic focus in all of their surgical candidates. By 1993 at the National Hospital for Neurology and Neurosurgery, London, UK, less than 10% of patients within the epilepsy surgery programme underwent depth electrode insertion [122]. This group [123,124] and others [122] have also described various computer-assisted methods to register the electroencephalography epileptic focus accurately in stereotactic space, integrated with both MRI and CT.

Other non-invasive imaging modalities can also supply information traditionally obtained from depth studies. In Engel's study from UCLA [125], 153 cases were reviewed in which depth electrodes had been used alongside ictal telemetry and fluorodeoxyglucose (FDG)-PET. The conclusion drawn was that when PET and telemetry information were concordant (and this was the case in over 80% of patients), stereotactic electroencephalography (i.e. electroencephalography recordings from depth electrodes that can be localized highly accurately within the three-dimensional stereotactic space) did not supply further information that would have changed clinical management decisions.

With modern MRI protocols, depth electrode recording should be unnecessary in over 95% of patients with hippocampal sclerosis being evaluated for temporal lobe surgery [1].

Depth EEG records from otherwise functionally inaccessible cortex. At present, depth electrode implantation is used in three main areas. First, depth electrodes can be used to determine from where seizures are arising in patients with MRI evidence of a lesion but otherwise discordant investigations [1]. Second, they can be used to determine where seizures are arising in patients in whom MRI shows dual pathology and the scalp EEG is indeterminate. Lastly, however, the major growth area for intracranial recording is in MRI-negative cases in which other functional imaging modalities and electroencephalography have suggested a possible focal source. In these circumstances the use of intracranial electroencephalography is probably mandatory until the sensitivity and specificity of these alternative investigations is more accurately known. In this way, depth electrode studies continue to play an important defining role in the investigation of potential surgical candidates.

While depth electrode studies continue they provide basic science data concerning epilepsy. However, not only are other modern techniques perhaps more suitable in the investigation of the majority of surgical candidates, but depth electrode insertion also has the inherent disadvantage of being invasive and therefore not without risk.

In 1987, Van Buren [126] described the complications arising from 2674 electrode implantations from 14 centres in the pre-MRI era. There was no mortality but there were 12 intracranial infections and seven intracranial haemorrhages with permanent neurological sequelae. In addition, there were two cases of Creutzfeldt–Jakob disease in patients in whom electrodes had been reused. Other groups have reported complications such as extra-axial haematoma and strip electrode placement within the white matter or within a cerebral sulcus [121]. One further disadvantage is expense, with each study costing at least £10 000 in the UK (including disposable platinum electrodes, 1–2 weeks' hospital stay with continuous telemetry, theatre time and other workforce implications). However, it is likely that invasive monitoring will retain a place in the minority of epilepsy patients whose presentation is not straightforward but in whom it is worth considering surgical treatment.

Stereotactic neurosurgical techniques provide the means of performing such invasive monitoring as safely as possible. Using CT [122] or MRI [121,127] guidance, the desired position and trajectory of each electrode within the brain can be accurately calculated and insertion can then be safely performed. Occasionally, stereotactic angiography or magnetic resonance angiography (MRA) data are integrated within the planning procedure in order to avoid major blood vessels during surgery. This is particularly useful when large numbers of electrodes are to be inserted into the anterior temporal region, Sylvian fissure area or insular cortex, as the risk of haemorrhage is directly related to the number of electrodes inserted.

When investigating a possible temporal lobe onset of epileptiform activity, most centres performing depth electroencephalography studies have tended to use two to four temporal electrodes passed orthogonally from lateral to medial through the temporal neocortex and deep white matter to the hippocampal formation (Plate 78.4). Spencer *et al.* [128], however, generally pass just one electrode longitudinally through the temporal lobe from the posterior temporal region in order to achieve the same end. The electrodes are not totally rigid and, although they can generally be placed to within 5 mm of the intended target, accuracy is inevitably limited by their flexible nature; therefore, postoperatively it is advisable to check the electrode positions that have actually been achieved. Although it is not often critical where the electrodes have been placed for recording purposes, it is essential for the neurophysiologist to know where they are placed in order to interpret the EEG correctly. Therefore, postoperative plain radiographs under stereotactic conditions or MRI may be performed. This makes it possible to determine the exact electrode position and then to translate this corrected position to the planning neuroradiological imaging modalities of MRI and CT. The disposable platinum electrodes in use at present also have the added advantage of being MRI compatible, which allows postoperative MRI studies to be performed with the electrodes *in situ*.

Depth electrodes can be placed with frame-based systems [121]. The added fixation and support that this provides is seen as its major advantage. However, depth electrodes can be placed using a frameless technique, with the use of flexible guide arms to stabilize the drill and the electrode as it is advanced [129]. The technique can thus decrease the operative time and potential risks to the patient [130,131]. The advent of frameless image-directed systems has led to relocatable head frame devices becoming obsolete in this regard [132,133].

Treatment

Stereotactic amygdalohippocampectomy

Although anterior temporal lobectomy remains the standard operation in most neurosurgical centres performing epilepsy surgery for hippocampal sclerosis, there is a trend towards more focal procedures (in part reflecting the neurosurgical trend towards minimally invasive surgery [12]).

Anterior temporal lobectomy is well tolerated but sometimes leads to a bony defect or the possibility of atrophy of the temporalis muscle, and patients also experience discomfort after surgery while chewing. In addition, neurological deficits, including visual field defects, memory impairment and language problems, have also been attributed to this approach [129].

The concept of a selective resection of the mesiobasal temporal structures was introduced by Neimeyer in the mid-1950s [134]. He described a transcortical, transventricular approach through the second temporal gyrus to reach the hippocampus at the amygdala. Several methods have now been described for selective mesiobasal resections, on the basis that lateral neocortical resection is unnecessary for seizure control and can cause postoperative memory problems [128,135–143]. Some authors argue that the lateral aspect of the temporal lobe, which is typically normal on pathological evaluation, does not need to be resected. Furthermore, there is some evidence to suggest that resection of the lateral temporal structures may be responsible for postoperative neurological deficits and only the mesial temporal structures harbour the epileptogenic focus [144]. It is suggested that stereotactic selective amygdalohippocampectomy can be used as an alternative to anterior temporal lobectomy.

Wieser and Yasargil [145] described a pterional transsylvian approach to the mesial temporal structures, which they suggested improved outcomes. Others use a trans-sulcal approach, usually between the middle and inferior temporal gyri [129,135]. When Kelly *et al*. [140] initially described their technique for stereotactic amygdalohippocampectomy using the Compass stereotactic equipment, their approach was first via the occipital lobe and then suboccipitally because of the field defects that occurred through using the former route. Using this type of approach, the hippocampal formation is met along its axis and is entirely suitable for maximal resection. However, most authors have preferred the lateral approach in order to reach the anterior hippocampus and amygdala without damage to the posterior hippocampal structures. Inevitably there is some sacrifice of the neocortical structures using the lateral approach but much less than in a standard temporal lobe resection and potentially without the risk of incurring visual field defects. Yasargil and others [136,146] have also described selective amygdalohippocampectomy, but using solely microsurgical techniques and not stereotaxy.

In 1994, Oliver *et al*. [19] reported using the Viewing Wand (Elekta/ISG, Stockholm, Sweden) to perform selective mesial resections. The Montreal group successfully applied this device to selective mesial resections in a number of patients and found it useful not only in guiding the surgeon, but also in estimating the extent of the hippocampal resection. This paper also documented the successful use of this device in assisting lesionectomy, corpus callosotomy, neocortical resection and the placement of depth electrodes.

Because sulcal anatomy varies among individuals, frameless stereotactic guidance allows a small incision and craniotomy to be placed in the optimal location. This aids complete hippocampal resection though a keyhole approach. The image guidance and trajectory views are critical in gaining access to the temporal horn of the lateral ventricle, allowing visualization of the amygdala and hippocampus [147]. Successful surgery relies on adequate exposure. The most common mistake is inadequate inferior and anterior temporal exposure. The lower extent of the central sulcus must be reliably identified, and this is easily achieved with the aid of image guidance. On the dominant side, the cortical incision must be made in front of the central sulcus and preferably in front of the precentral sulcus. An errant trajectory can lead the surgeon to miss the temporal horn in the dissection through the white matter. A trajectory that is too anterior will pass by the anterior extent of the ventricle; an approach that is too dorsal could lead into the insula or temporal stem [135]. The extent of resection is also demonstrated intraoperatively with the use of neuronavigation.

Neuropsychiatric evaluations performed after selective procedures have suggested no new language impairment [129]. Selective operations are more difficult technically and there is a higher reported risk of vascular disturbance and hemiplegia but a lower risk of dysphasia and visual field defect [1]. Seizure control in these patients is encouraging [135,136,142,145].

Stereotactic craniotomy and lesionectomy

Perhaps the most common way in which stereotactic neurosurgery is utilized at present in the treatment of epilepsy is in the removal of epileptogenic lesions [148–151]. Many of those lesions that cause chronic epilepsy (as opposed to those high-grade brain tumours with a short history and mass effect, which have seizures as part of the clinical syndromes) are cortically based, small and would be difficult to find without some form of stereotactic image guidance.

Just as with tumours, certain vascular lesions [arteriovenous malformations (AVMs), cavernomas] may be difficult to localize if they are situated within deep brain structures. Stereotaxy may allow direct localization as well as localization of associated vascular structures feeding or draining a lesion. With AVMs, stereotaxy helps define both the superficial and deep limits of the nidus and can help ensure its complete removal [14]. Stereotaxy has also been used to assist transcallosal resection of hypothalamic hamartomas in patients with intractable epilepsy, assist in limiting the resection and minimize injury to the third ventricular floor and walls [152].

Stereotactic craniotomy has become a standard operation in epilepsy management, allowing epileptic lesions to be removed in minimally invasive ways (i.e. with ‘mini’ skull flaps and with minimal brain retraction, dissection and, hence, trauma). However, such methods are at odds with the techniques of traditional lesional epilepsy surgery in which electrocorticography and cortical stimulation are used with a view to *en bloc* resection of the surrounding cortex when this is considered to be epileptogenic. A basic principle of surgery for extratemporal neocortical epilepsy is that the wider the excision around an epileptic focus, the more likely it is that complete seizure control will be achieved [1]. Clearly, in this situation, a large craniotomy with a wide cortical

exposure is necessary. Stereotactically guided lesionectomy therefore implies a simple lesionectomy without removal of surrounding brain tissue in an *en bloc* fashion. The relative efficacy of simple lesionectomy and larger *en bloc* brain resections is controversial at present, and the issue must be considered unresolved at the present time [148,149,151,153,154]. Certainly, methods that maximize total lesion excision must be advantageous not only neuro-oncologically, but also in terms of seizure control.

In considering the practical surgical issues when a lesion is being explored under the operating microscope following image guidance, a border between it and surrounding brain has to be determined. Sometimes direct inspection will reveal a clear-cut margin or even a pseudocapsule. However, on other occasions the boundary will be less definite, and in these cases the trend is to remove more rather than to leave suspect or reactive tissue. Image-directed surgery can aid in directing this process. At present, the gold standard for resection of a lesion in the region of eloquent cortex is awake craniotomy with intraoperative cortical or subcortical stimulation [155–161]. Integrating frameless navigation with intracortical mapping can further enhance optimal tumour resection while minimizing morbidity, and this may be further improved in the future by incorporating tractography [52,91–97].

A further diagnostic and also technical issue for the surgeon is the fact that a large proportion of lesions causing chronic epilepsy (cavernous angiomas, dysembryoplastic neuroepithelial tumours, low-grade gliomas) are poorly defined on CT and often visualized solely on MRI. In these instances image-directed surgery using MRI may be invaluable.

Although we have detailed above the specific instances in which stereotaxy may be used, it can be seen that its use may be applied to virtually all branches of epilepsy surgery. These include non-lesional focal resections, multilobar resections (including hemispherectomy) and functional procedures (such as multiple subpial transections and corpus callosotomy [162]).

Stereotactic ablation and stimulation for epilepsy

Lesion-making in the central nervous system (CNS) may be performed using a variety of methods, which, except in one instance, require the opening of the skull and the passage of a needle into the brain substance. The actual method for producing focal brain necrosis can be chemical (absolute alcohol), freezing (using a cryoprobe) or by heating. Radiofrequency thermocoagulation is the most widely used method as it is flexible, yet repeatable, and quick to use. The one closed method of lesion-making in the CNS that is completely non-invasive (in a surgical way at least, as there is a small but definite risk of radiation-induced necrosis of the surrounding normal brain) is stereotactic radiotherapy or radiosurgery.

Both stereotactic ablation and stimulation have been used for many years, in small numbers of patients, in an attempt to control or modify seizures. Targets have included the amygdala, various thalamic nuclei, the fields of Forel, the anterior commissure, the fornix and the posterior limb of the internal capsule [163–172].

Although there are numerous articles in the literature describing stereotactic procedures in the management of epilepsy, analysis of these is complicated by a number of factors:

- Most studies were undertaken in advance of the establishment of a uniform classification of seizures, making it difficult to determine the seizure disorder treated by a particular lesion.
- Often, multiple subcortical targets were used in individual patients, making it difficult to assess the role of a specific target for a specific condition.
- There is sufficient variability in the location of subcortical nuclei with respect to internal reference points that in many cases it is uncertain whether unsuccessful surgery was a result of inaccurate localization, incomplete destruction or inappropriate selection of target.
- There has been a tendency to reserve stereotactic surgery for particularly complex intractable seizure and behavioural problems. This philosophy may have eliminated some of the more straightforward disorders for which the procedures may have been effective [144].

In 1970, Narabayashi and Mizutani [173] described the use of radiofrequency stereotactic amygdalotomy (i.e. a direct but very focal ablation of the epileptic focus) in 25 patients with a 1- to 6-year follow-up. Some had unilateral and some bilateral lesions performed mainly for behavioural problems as the primary indication for surgery. Nine patients (36%) had complete abolition of electroencephalography and clinical seizures, nine had reduction in seizures (36%) and seven had no change (28%). Several other authors have described their experience with stereotactic radiofrequency amygdalotomy [174–181].

Talairach and Szikla [182] used 'stereoencephalographie' to localize the amygdalohippocampal complex and then ablated these structures with yttrium-90. Fifteen cases were described in which an epileptic focus was ablated using stereotactically implanted yttrium-90 pellets to cause a localized necrotizing lesion. Pellets were routinely placed in the anterior commissure, with the rationale of preventing spread to the contralateral temporal lobe. Using this regimen, nine patients were rendered seizure free (with short follow-up of 7–14 months), two were improved and four showed no change.

There are few reports in the recent literature regarding stereotactic lesioning for the treatment of epilepsy. Patil *et al.* [183] described multiple interventions for epilepsy in 24 patients with seizures of multilobar origin. Their technique involved a combination of topectomy, multiple subpial transection and/or amygdalohippocampal radiofrequency ablation (amygdalohippocampotomy). Three of their patients with seizures of medial temporal origin underwent stereotactic amygdalohippocampotomy with good results (seizure free or rare seizures). This procedure involved CT-guided identification of the amygdala and hippocampus for stereotactic targeting. A radiofrequency lesion measuring 11×15 mm was then made in each of these structures [175].

Parrent and Blume [184] performed stereotactic amygdalotomy in 19 patients with temporal lobe epilepsy. All patients were shown to have mesial temporal originating seizures by continuous electroencephalography monitoring with or without subdural electrography, and all recorded seizures originated from the temporal lobe that was ultimately subject to the ablation. Surgical planning involved the identification of the amygdala and

hippocampus on stereotactically acquired MRI scans and postoperative MRI confirmed the accuracy of targeting. In five patients who underwent limited lesioning (mean 6.4 lesions, range 4–9) a favourable seizure outcome (defined as seizure free, auras only or >90% seizure reduction) was obtained in only one patient (20%). However, 15 patients underwent extensive lesioning that was designed to produce a large confluent area of ablation (mean 26 lesions, range 12–54). In this group, nine (60%) achieved a favourable outcome and postoperative MRI demonstrated extensive ablation of the amygdala and hippocampus, sparing the parahippocampal gyrus.

The results of these operations had in general been disappointing and this type of surgery had been largely abandoned until recently. The outcomes were not as good as one would expect following temporal lobectomy or selective amygdalohippocampectomy in a similar group of patients. Therapeutic success was unpredictable and often not without a significant risk of complications. Hence, the overall clinical impression of these procedures was that good outcomes were patchy and difficult to predict, and that the improvements not sustained.

Several strategies can be pursued with stereotactic and functional surgery. The first is to destroy the seizure focus in a minimally invasive manner. Such a targeted approach requires strong physiological evidence of the seizure focus, together with as precise as possible anatomical delineation with modern imaging. A second strategy is to decrease the epileptogenic volume, in this way reducing seizure burden and, at least in theory, putting intrinsic brain mechanisms, as well as anticonvulsants, in a better position to deal with the epileptic tendency. A third use of stereotaxy is for the interruption of the pathways of seizure propagation. Because of the high precision of these techniques, discrete axonal projections can be interrupted, thereby disconnecting the seizure source from adjacent or remote brain structures. Further strategies that are possible with stereotactic neurosurgery are the destruction or modulation of brain structures, which may have an influence on seizure tendency; thalamic lesioning/stimulation may reduce cortical excitability and thus epileptogenesis [185].

A recent resurgence of interest has occurred, encouraged both by the improved anatomical precision of stereotaxy made possible by MRI and better surgical stereotactic instrumentation and also by the success of these procedures in other conditions, such as for Parkinson's disease and pain [186].

Traditionally, functional neurosurgery has relied upon frame-based stereotactic techniques. Recent developments in this field have included the incorporation of brain atlases and microelectrode recording devices into the registration of radiological data of image guidance systems to aid target identification.

The improvements in imaging have worked in concert, with an increased understanding of the pathophysiology of epilepsy disorders such that the identification and selection of targets has a stronger scientific rationale than was previously available. There is also research interest in the possibility of stem cell transplantation and stereotactic drug implantation [1]. The trend towards minimally invasive surgery has led to a re-examination of stereotactic functional procedures. Stereotactic procedures have the possibility of being highly accurate, more economical and better tolerated than conventional craniotomy and resective surgery.

Stereotactic radiosurgery

Radiosurgery is a minimally invasive technique designed to elicit a specific radiobiological response at the target tissue using focused ionizing radiation delivered in a single procedure. The underlying scientific principles, history and current indications for stereotactic radiosurgery are beyond the scope of this chapter and are reviewed elsewhere [187–191]. The technique was pioneered by Lars Leksell at the Karolinska Institute in Stockholm, and devised to treat intracranial lesions by delivering a high dose of radiation precisely at the intracranial target using stereotactic guidance. A variety of different radiosurgery techniques have been developed during the past 40 years. Refinements in stereotactic methodologies, major improvements in dose planning software, and advances in neurodiagnostic imaging have all facilitated the increasingly broad application of radiosurgery. Numerous studies have examined the benefits, risks and long-term results of radiosurgery and support it as a non-invasive alternative for several disorders, including vascular malformations, tumours, trigeminal neuralgia, movement disorders and, perhaps, epilepsy. However, a recent review of the literature on stereotactic radiosurgery by Pollock [192] using evidence-based standards suggests that caution must be used when interpreting many of these studies, as the vast majority of published papers on stereotactic radiosurgery are of level 3 evidence or below. Pollock also concluded that, for various reasons, it is unlikely that randomized clinical trials will be performed to evaluate stereotactic radiosurgery. Nonetheless, the preponderance of level 3 evidence supports the role of radiosurgery as either an adjunct or alternative to surgical resection or fractionated radiation therapy.

The role of stereotactic radiosurgery in epilepsy is reviewed elsewhere in detail [193–195]. However, although stereotactic radiosugery is the only non-invasive surgical form of treatment for epilepsy, it also has some limitations. It relies exclusively on anatomical targeting, as neurophysiological confirmation of the target structure is not possible. Furthermore, lesion sizes may vary and shielding adjacent radiosensitive neural structures may be difficult. Integration of three-dimensional corticospinal tractography (Plate 78.5) into treatment planning for gamma knife surgery may help plan targeting and reduce morbidity as a result [98,99]. Intraoperative MRI in conjunction with stereotactic radiosurgery has also been described [196].

Radiosurgical techniques are used to create image-guided physiological inactivity or focally destructive brain lesions without neurophysiological guidance [197]. It allows, in a single session, the precise and complete destruction of chosen target structures containing healthy and/or pathological cells [198]. It is the only remaining stereotactic technique for the treatment of epilepsy that still involves the use of a stereotactic head frame fixed to the patient's head with screws, rather than the image-based, intracranial navigation independent of an external frame.

Leksell [199–201] originally designed his gamma knife (in which multiple beams of gamma (γ)-rays are focused to a single target using traditional stereotactic methods) for functional neurosurgery. He realized that deep epileptic foci could become targets, especially with future advances in functional imaging.

At present, however, little functional radiosurgery is performed worldwide – probably less that 2% of all radiosurgical proce-

dures, the vast majority of which are carried out for arteriovenous malformations, benign tumours such as acoustic neuromas or treatment of solitary cerebral metastases. The availability of high-quality, three-dimensional imaging with MR (for precise targeting of normal structures) and evidence of some limitations regarding drug efficacy have now prompted a reappraisal of gamma knife surgery for functional disorders [202–207]. In the past decade, the number of studies in which radiosurgery has been described in experimental epilepsy and in clinical situations has increased significantly.

Heikkinen *et al.* [208] illustrated that although 16 out of 29 patients with AVM (55%) had improvement in their seizures following proton beam irradiation, only 17% of these demonstrated angiographic obliteration. Furthermore, three out of five patients with complete obliteration, five out of seven partially obliterated patients and 8 out of 17 non-obliterated patients became seizure free.

Between 1970 and 1984, Steiner *et al.* [209] treated 247 patients with AVM using gamma knife surgery. Out of the 247 patients, 59 had epilepsy; in the majority of these patients (52), seizures improved significantly. The cessation of the seizures appeared to commonly occur several months before the occlusion of the arteriovenous malformation.

The Sheffield radiosurgical group have described the effect of radiosurgery on 160 of their 507 patients with AVM who had been followed for 2 years [210]. In this group, 48 (30%) had epilepsy on presentation. On follow-up, 38% of these patients were seizure free, 22% had improved seizure control and 6% had increased seizures.

The results from most other centres performing radiosurgery for AVMs are similar, i.e. that radiosurgery to prevent rebleeding from AVMs does have some beneficial effect on seizures in a proportion of cases and that the effect may well be independent of any obliteration of the AVM itself [209,211–214].

Cavernous haemangioma is a benign vascular hamartoma of the CNS, which most frequently presents with epilepsy [215]. Some authors have reported a reduced risk of rebleeding after gamma knife surgery [216], whereas others have reported no effect [217,218]. Bartolomei *et al.* [219] conducted a retrospective multicentre study to evaluate the effectiveness of gamma knife radiosurgery in the treatment of drug-resistant epilepsy associated with cavernous haemangiomas. A total of 49 patients were studied (26 male and 23 female), with a mean age of 36 ± 10 years. The mean duration of epilepsy before gamma knife radiosurgery was 7.5 ± 9.3 years. The mean frequency of seizures before gamma knife radiosurgery was 6.9 episodes per month. The cavernous haemangioma was located in the temporal lobe in 23 cases, and in extratemporal cortex in the remaining 26 cases. The mean margin dose to the lesion was 19.2 ± 4.4 Gy (range 11.3–36 Gy). The volume was 2370 ± 2211 mm^3 (range 110–10 296 mm^3). No complications were reported on the day of the radiosurgical procedure. With a mean follow-up of 24 ± 13 months, 26 patients (53%) were seizure free (Engel class I). Of these, 24 patients were in class IA, and two patients with occasional auras were in class IB. A highly significant decrease in the number of seizures was achieved in 10 patients (20%) with class IIB status. The remaining 13 patients (26%) showed little or no improvement in their seizures.

In the seizure-free group, the mean delay between gamma knife treatment and complete remission was 4 months (range 0–9 months, median 6 months). This study demonstrated that the prognosis for seizure control depended on the type of epilepsy and location of the cavernous haemangioma. The outcome was better for patients with simple seizures than for those with complex partial seizures. The location of the lesion was the most significant. In the 14 patients whose lesion was located in the mesial temporal region, 12 showed a poor outcome of treatment. Lesions in the laterotemporal region were associated with a good outcome (six out of seven patients). A location in the central region was associated with an excellent outcome, all four patients in this group remaining seizure free. For other locations, results were unpredictable. A possible explanation for the difference in prognosis is that the epileptic network in the medial temporal region is more complex and diverse, and hence more difficult to ablate completely and accurately than in the extratemporal and indeed in the more central regions. Regis *et al.* [220] and Hsu *et al.* [221] have also reported that gamma knife and linear accelerator radiosurgery, respectively, are an alternative treatment to conventional surgery for epileptogenic cavernomas, particularly when the lesions are located in the central regions or eloquent areas of the brain. The disappearance of seizures following conformal radiotherapy [222] and conventional radiotherapy [223,224] of tumours has also been reported.

In March 1993, in Marseilles, Regis *et al.* [225] used gamma knife surgery to treat the first patient with medically refractory mesial temporal lobe epilepsy with hippocampal sclerosis. The group described that the entorhinoamygdalohippocampectomy was performed with the gamma knife at low marginal dose (25 Gy), a dose that later caused target necrosis. The 7000 mm^3 approximate volume represented the largest functional target irradiated until that time. This patient has remained seizure free with no associated complications. Since then, around 130 patients have undergone epilepsy surgery using the gamma knife in Marseilles [194], all in the context of a successive prospective controlled trial.

This group have also studied the optimal parameters for the treatment of epilepsy without space-occupying lesions using the gamma knife [198,226]. In this study, they recruited seven patients (four men and three women) who had medication-resistant mesial temporal lobe epilepsy. The mean duration of this disease was 27 years (range 16–35 years), and mean age at gamma knife surgery was 33 years (range 25–40 years). They used MRI for target localization. The mean calculated volume of the target was 6500 mm^3 (range 6350–6900 mm^3). According to the volume of the target, they used a dose margin of 25 Gy at the 50% isodose line. The range of patient follow-up was 24–61 months. They noticed a dramatic effect on seizure frequency around 10 months postoperatively (range 8–15 months, mean 10.2). This was coincident with the development of MRI signal changes, followed by atrophy in the related structures. All but one patient became seizure free. The authors suggested that there was a direct relationship between the quality of the results from gamma knife surgery and the dose and volume of the procedure.

In their current protocol, Regis *et al.* [227] describe the target being covered by two 18-mm collimators, with a dose of 20–25 Gy at the 50% marginal isodose line, the target volume being

6500–7000 mm^3. In this study, 25 patients were treated according to this protocol, and the follow-up of the entire group varied between 6 and 72 months. The median latency for seizure cessation was 10.5 (range 6–21) months. With the exception of two patients who immediately became seizure free, the median latency for aura cessation was 15.5 months. There was a gradual decrease in the frequency, intensity and duration of seizures in the other 23 patients. Low-dose steroids reduced reported side-effects, such as headaches, nausea and vomiting.

Regis *et al*. [228] have reported good results after Gamma Knife surgery in temporal lobe epilepsy; however, Srikijvilaikul *et al*. [229] reported failure of gamma knife surgery for mesial temporal lobe epilepsy, and a recent study by Hoggard *et al*. [230] on the clinical course and neuroradiological correlates after stereotactic radiosurgical amygdalohippocampectomy with neuroradiological correlates also demonstrated disappointing results compared with temporal lobectomy or selective amygdalohippocampectomy.

In 1994, Barcia-Salorio *et al*. [231] provided a long-term analysis of a series of 11 patients with temporal lobe epilepsy, who were treated with stereotactic radiosurgery using a dose range of 10–20 Gy. Of these patients, five experienced complete cessation of seizures, and an additional five were improved. Seizures began to decrease gradually 3–12 months after radiosurgery. These authors noted that the main difficulty encountered was the correct localization of the epileptogenic focus. Recent papers from the Marseilles group describing long-term results in 15 patients with mesial temporal lobe epilepsy with over 2 years' follow-up [232] and over 5 years' follow-up [233] have shown results similar to conventional surgery.

Lindquist *et al*. [207] have also described the use of the gamma knife for the radiosurgical treatment of epilepsy. They report six patients with complex partial seizures, all of whom had a reduction in seizure frequency.

Heikkinen *et al*. [234] treated a single patient with temporal seizures by stereotactically irradiating the pes hippocampus. A lower radiation dose of 10 Gy was used and the MR scan at 30 months showed no change to the radiated structures. Seizures ceased 7 months after treatment and had not recurred by 27 months.

In addition, there have been reports of the use of radiosurgery to treat gelastic seizures associated with hypothalamic hamartomas [202,206,227,235–239] and to achieve a functional corpus callosotomy [240,241].

Radiosurgery at doses that produce atrophy presumably work through destruction of the epileptogenic target. However, the mechanism of efficacy of lower dose radiosurgery is not known, but possibly involves changes in the neuronal network involved in seizure generation [144].

The current evidence suggests that stereotactic radiosurgery can be effective in treating focal epilepsy. This form of treatment is closed, tractless and bloodless [242]. More importantly, the current advances in both diagnostic and functional imaging, and improvement of the therapeutic rationale (i.e. directing the radiosurgery towards the epileptogenic lesion itself, rather than interrupting perceived pathways of seizure spread) may improve results further.

The optimal dose selection (necrotizing versus non-necrotizing), methods of non-lesional epilepsy localization, and target volume for irradiation have still to be determined [197,203,205,243]. It is not known what type of tissue effect is required to stop the generation or propagation of seizures. Some studies have shown that low doses (below 20 Gy) are ineffective for the radiosurgical treatment of epilepsy [203,205]. On the other hand, high doses (as much as 100 Gy) can cause target necrosis and regional brain oedema [244].

Potential advantages

- No surgical incision.
- Decreased morbidity and increased patient comfort.
- High accuracy.
- Accessibility of deep sites.
- Potential efficacy in non-resective surgery.
- Single-day stay in hospital.

Limitations

- Delayed response.
- Volume constraints.
- Fewer predictable outcomes than resective surgery.
- Uncertain long-term effects.

Conclusion

Lesion-making in the CNS has a limited role at present, but it is anticipated that the use of stereotactic radiosurgery will become more attractive in the future. Stereotactic lesioning in the medial temporal lobe has produced favourable results in a number of patients. However, the decrease in seizure frequency is not as dramatic as that following temporal lobectomy in properly selected cases. These techniques continue to undergo modification and will require further review in the future. The use of radiosurgery for lesion production is less invasive than radiofrequency ablation and may prove to be safer. Radiosurgical trials in selected epileptic syndromes have shown highly promising, although still preliminary, results. If focal hippocampal (or any other brain tissue) irradiation can eliminate seizures without the need for complete tissue destruction then radiosurgery may become an important therapy for patients with intractable epilepsy.

The future of frameless stereotaxy will include better registration techniques and more accurate positioning of the probe tips in space, along with the integration of further functional imaging modalities. Video and heads-up displays within the surgical microscope will offer increasingly direct and accurate feedback to surgeons. The development of intraoperative imaging techniques will allow real-time anatomical updates to be preformed to compensate for brain shifts associated with the surgical procedure. Intraoperative MRI will facilitate resection of abnormal brain tissue and brain tumours by allowing residual tissue to be identified before closing the case.

The power of computers to generate three-dimensional renderings will also continue to improve. The inclusion of 'picture in a picture' technology in head-mounted displays will allow computer-generated three-dimensional images to be displayed adjacent to the surgeon's field of view, providing simultaneous projection of the surgical field and stereotactic images. The

merging of multimodality imaging into neuronavigation systems will allow neurosurgeons to invstigate and treat increasingly complex epilepsies.

Although stereotaxy and neuronavigation will never be a replacement for surgical skill, it is a powerful weapon in the armamentarium of contemporary neurosurgeons.

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79 Complications of Epilepsy Surgery

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Introduction

Presurgical assessment involves invasive procedures and the complications arising from these procedures have to be considered. It is known that with certain procedures physical side-effects are inevitable and these will be included as well as those that are unexpected. Procedures such as craniotomy carry general complications, for example haemorrhage and infection, which will be dealt with briefly. More distant possible effects, such as deep vein thrombosis and pulmonary embolus, will not be dealt with except where relevant. Certain groups may be more at risk, for example patients on valproate may have a low platelet level causing a bleeding disorder [1]. In particular, major procedures in young children may carry additional hazards. Modern transparency has made it possible to talk about a learning curve that is experienced in performing invasive procedures and operative techniques when new centres are set up or personnel replaced and this has a bearing on the complication rate [2].

Complications of invasive procedures for presurgical assessment

Carotid amytal test

In the usual and simplest form of the intracarotid sodium amytal test (ISA) the internal carotid arteries are cannulated via the femoral artery, the usual technique for cerebral angiography, which is generally free of complications; the incidence is likely to be lower in patients undergoing presurgical assessment because in general they are young and free of arterial disease. Although large numbers of patients undergo this test, comprehensive data are sparse. In 1993, Rausch *et al*. reported ISA practice having canvassed 71 epilepsy surgery centres and received replies from 68. There was no mortality and in 40 centres there was no morbidity; in 12 centres the morbidity was less than 1% and in the remaining centres the highest morbidity was 5% [3]. Loddenkemper *et al*. [4] describe the incidence of carotid artery dissection (CAD) in these patients. In 435 consecutive intracarotid amobarbital tests (IAT) three patients with a CAD were found (0.7%). The mean age of patients with dissection (51.3 years) was higher than the average age of the 432 patients without dissection (31.7 years) ($P < 0.05$). All patients had clinical symptoms including face or neck pain.

Twelve centres described a selective test in which smaller arteries were cannulated in an effort to avoid some of the theoretical and practical disadvantages of the standard test. Eight of these centres had no morbidity but in four centres there was significant morbidity, the highest being 8% [4]. Jack *et al*. [5,6] first described selective catheterization of posterior cerebral branches but this has given rise to some complications and they abandoned the procedure. There were no problems described with the alternative procedure used by Wieser in Zurich [7]. More recent papers indicate that technical changes in the procedure, including the use of microcatheters and of fluoroscopic tracking systems, have improved the safety of these procedures [8].

In testing for bilateral secondary synchrony, it may be necessary to administer large amounts of intravenous barbiturate anaesthetic, even to the point of producing a silent electroencephalogram (EEG). There should be careful consultation with the anaesthetist about the care and monitoring of these patients – especially their airway – during the test and recovery.

Invasive procedures for placing electrodes

Recording and documenting seizures by videotelemetry, irrespective of the electrodes used, can be troublesome. Constraints of time and finance usually make it necessary to reduce the patient's anticonvulsant medication or even remove it completely. This can result in partial status, secondary generalization of seizures and, occasionally, status epilepticus. These may be accompanied by confusion for which the patient may be amnesic or, occasionally, a postictal psychosis that may require treatment in addition to the restoration of anticonvulsant medication.

It is convenient to discuss two points of general interest here. Most departments will refuse to use MRI to examine patients who have steel or nichrome electrodes in place. Zhang *et al*. [9] has shown that there is no undue heating of these electrodes in a 1.5-T MR scanner, and the Yale group have reported a substantial series in which no complications have been observed [10]. We have successfully used MRI to image platinum-based electrodes without any apparent difficulty. Our neuradiologists examine plain radiographs to assess the proximity of electrodes and the possibility of their crossing before the MRI is performed. The second problem is the possibility of introducing slow virus diseases, such as Creutzfeldt–Jakob disease, as was reported with the reuse of electrodes in 1977 [11]. The only way to avoid this is never to reuse the electrodes.

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Minor invasive techniques

There are three techniques, which use the following types of electrodes: sphenoidal, epidural peg and foramen ovale.

Sphenoidal electrodes

These are effectively extracranial electrodes and serious complications are rare. Convulsive syncope has been reported during insertion [12]. Fluoroscopic placement of the electrodes reduces complications [13]. Transient facial palsy after placement of sphenoidal electrodes has been attributed to the effect of the local anaesthesia on peripheral branches of the facial nerve [14].

Epidural peg electrodes

These are not commonly used. Pilcher *et al.* [15] quote a personal report by Wylie in which bacterial colonization was seen in 22% of cases, a haematoma on CT in one patient and two patients were rendered sufficiently anaemic to need a blood transfusion [15]. There is a more recent report of a focal parenchymal haemorrhage under the site of an epidural peg electrode, revealing itself as a transient epileptic focus [16].

Foramen ovale electrodes

These are placed through the foramen ovale, through the fibres of the trigeminal nerve, to lie in the subarachnoid space in the ambient cistern. The method was introduced by Siegfried *et al.* [17] and taken up by a number of other groups. We ourselves have used this method in over 200 patients. Most centres regularly use smooth multicontact electrodes, inserted through an appropriate needle. The possible complications include nerve damage during insertion, haemorrhage within the subdural or subarachnoid space (usually of no significance), misplacement of the electrode within the cerebral substance and infection. In our patients the commonest problems were facial swelling and transient pain or numbness in the trigeminal territory. In our patients a small number (less than 2%) were left with permanent numbness in the trigeminal territory and only one with persistent facial pain. Known penetration of the brain with clinical consequences occurred on four occasions, two with serious consequences. In one case there was a disorder of eye movement, which recovered completely, and in the other there was a capsular haemorrhage that resulted in a permanent hemiparesis. Schuler *et al.* [18] reported serious consequences in patients who have undergone previous temporal surgery. In five of our cases there was frank meningitis, including one case of unsuccessful insertion, all of which responded to appropriate treatment. In a recent account, Wieser [19] notes that in 264 patients there was one serious subarachnoid haemorrhage and two cases of symptomatic subarachnoid haemorrhage. There were two cases of meningitis, both treated successfully. Facial pain was experienced in 19% and other minor and transient effects in less than 10%. A recent report of 331 insertions in 329 patients was given by Pastor and colleagues [20]. Complications were seen in 6.64% of procedures but were severe in only 1.81% of patients (clotting or intracranial haemorrhage); four of these were asymptomatic, one patient developed status epilepticus from which she eventually died, and the other patient, who had a haemorrhage into the fourth ventricle, developed hydrocephalus and required a shunt.

Major invasive techniques

Subdural strips and grids

Most centres now use commercial electrodes; well made, flexible and manufactured from platinum, these are available in many configurations from strips containing only four contacts in line to large arrays of 8×8 with a total of 64 contacts. The complications increase with increasing size and number of contacts and duration of implantation. In all patients with indwelling electrodes we have used antibiotic cover from the time of insertion until at least 24 h after removal.

We prefer subdural strip electrodes to foramen ovale electrodes because the minor complication rate is less and the coverage of the temporal structures is more flexible. In over 100 bilateral subdural strip implantations we have encountered only one problem. An acute subdural haematoma probably arose from rupture of a bridging vein, associated with coughing and vomiting during recovery from anaesthetic. Regrettably the patient was left with a significant neurological deficit. Wyler and colleagues [21] report no such complications in 300 cases.

More complications arise with larger subdural mats. Ninety-three patients have been implanted in our centre with 20, 32 or 64 contact mats and significant complications were seen in 22 patients (23.6%). The commonest complication was infection in 12 patients (12.9%), followed by transient neurological deterioration in seven patients (7.5%) and significant subdural haematomas in only two patients (2.1%). The origin of the changes induced in the underlying brain by subdural grids is complex. Stephan *et al.* [22] report a picture of aseptic meningitis which is severe in 27%. Local cerebral swelling can be a problem, especially in patients who have been previously operated at that site and in whom tedious dissection of adhesions has been necessary. Most of the infection is locally within the wound, invariably in the extradural space, and clear meningitis or encephalitis has not been seen.

In recent literature the authors do not report strip and grid electrodes separately. Reports of implantation in adults and children do not show a significant difference between them. In substantial series the incidence of extradural haematoma is 1–2% and of subdural haematoma around 1% [23–25]. Many of these haematomas are asymptomatic and require only conservative treatment. The incidence of infection in the same reports is around 1–2%; the use of prophylactic antibiotics is universal. The incidence of cerebral oedema and raised intracranial pressure is similar and steroids are not universally used. Araki *et al.* [26] studied 37 patients divided them into treated and control groups and found that the incidence of cerebral swelling on CT was greater in the control group. A surprising finding is mortality from subdural grids. In the Fountas series two patients died: one as a result of raised intracranial pressure and the other following an aspiration pneumonia. In another series there was one death during grid insertion.

Intracranial depth electrodes

Centres using these electrodes report an infection rate of about 2%. In 1993, Pilcher [15] reported 1.4% in 1582 patients pooled from eight centres. The risk of haemorrhage depends upon the technique (which determines the direction of track, and therefore

the structures at risk) and also the number of electrodes used. Insertion techniques use three routes: the orthogonal, axial and posterior approaches. In the orthogonal approach, especially around the insula in the temporal lobe, the major vessels are at risk and some groups insist that angiography is necessary. The axial approach tends to pass through areas that have fewer major vessels. The posterior approach, devised by Spencer [27], has produced visual field defects. Data from Pilcher in 1993 suggested that the orthogonal approach (1–2%) was safer than the axial approach (2–3%), possibly because of the use of angiography [15]. Clinically significant haematoma arose in 3 out of our 57 patients (5.2%). However, with changes of technique and materials we believe that the risk has diminished to those described by other groups. Merriam *et al*. [28] showed that MRI abnormalities could be found along the track of 67% of depth electrodes, although in only one was there evidence of a significant parenchymal haemorrhage [28]. A recent report describing the use of all kinds of intracranial electrodes, including deep brain stimulation (DBS) and radiofrequency (RF) electrodes, records an incidence of symptomatic haemorrhage of 1.2% and of permanent neurological deficit of 0.7% [29]. Guenot *et al*. [30], describing the use of stereo-electroencephalography (SEEG) in 100 consecutive patients, implanted a total of 1118 electrodes. There were five complications: two electrode breakages, two infections and one haematoma that was fatal.

Summary

Presurgical evaluation has both physical and intellectual complications, which are generally dependent upon the invasiveness of the procedure and experience of the centre, and our complication rate has improved with time. Deaths are extremely rare. Significant physical complications occur with more complex interventions in less than 5% of cases and the general level is 1–3%.

Therapeutic procedures

Introduction

In general, candidates for epilepsy surgery, except for some children, are free of chronic or severe medical problems. A high proportion of these procedures are intracranial and are therefore subject to the usual complications of craniotomy. In brief, and except where detailed under the individual procedures, they comprise haematomas (extradural, subdural and intracerebral), infection, possibly hydrocephalus and, rarely, air embolism and pulmonary embolism. These complications usually respond to appropriate treatment and do not influence the outcome of the surgery.

In modern epilepsy surgery operative mortality is commendably low. In the King's/Maudsley series from 1976 to 2001 there were 818 procedures resulting in seven perioperative deaths (0.86%) and 20 late deaths (2.4%) The late deaths were associated with seizures in 15 patients (75%) and, although many patients had poor seizure control, there were six patients in group 1A who died in their first postoperative seizure, in some cases in the course of antiepileptic drug (AED) reduction.

Typical figures from pooled data in 1993, and from an International League Against Epilepsy (ILAE) survey, suggest a perioperative mortality of between 0.5% and 1%, with some centres having no deaths at all [15,31]. In a long series of patients from Vellore there were no deaths since 1960 [32], and in 654 procedures from Sweden between 1990 and 1995 there was only one death from haematoma [33]. A series from Bonn describing patients who were operated on over a period of 6 years reported no deaths [2]. The *Comprehensive Textbook of Epilepsy* suggests that the perioperative mortality rate is currently less than 0.2% [34]. Late mortality does not require further discussion.

McClelland and Hall [35] report the overall infection rate in 2111 neurosurgical patients. In intracranial cases, this was 0.8%, close to the 0.5% reported by Pilcher *et al*. [15]. In a series from Bonn, the commonest complication was infection, which occurred in 21 out of 459 interventions including intracranial recording; there were 15 deep wound infections, requiring removal of the bone flap (3.5%), and six patients (1.8%) had meningitis (which probably caused hydrocephalus in three cases), which was relieved by shunting. There were no intracranial haematomas, except in the intracranial electrode implantations. The lowest complication rate was in temporal lobectomies (7.4%) and the greatest after hemispherectomies and multilobar resections (16.6%) [2]. In 128 temporal lobectomies in children, reported from Toronto, there were no significant surgical complications, including overt infection, although four patients with a fever were treated with antibiotics [36]. A paper by Oertel *et al*. [37] suggests that the use of neuronavigation in temporal lobe surgery for epilepsy reduced complications, including infection. In our series it is commoner when intracranial monitoring has been used. Occasionally, the patient appears to have meningitis or a meningitic reaction, but, more commonly, it appears in the extradural space, often involving the bone flap. No patient in our series has died or come to permanent harm from intracranial infection; it does not appear to affect the seizure outcome of the operation but the misery it can cause to all parties should not be underestimated.

Intracranial resective surgery

Frontal lobe resection

Proper technique should ensure no damage to the medial surface of the remaining hemisphere or its blood supply. Unless the resection encroaches upon the gyrus anterior to the precentral gyrus in a non-dominant hemisphere it is unlikely to produce any hemiparesis. Of course, in the dominant hemisphere, Broca's area must be respected and Comair *et al*. [38] recommend that such resections should be performed under local anaesthesia. Resection in or close to the supplementary motor area, which can now be identified preoperatively using functional MRI (fMRI) [39], has long been known to produce a severe motor deficit that resembles a conventional hemiplegia but is in fact a sort of volitional apraxia. There is a recent description in the paper by Bannur and Rajshekhar [40]. They, and other authors, also note mutism or degrees thereof [40,41]. All authors agree that the deficit invariably recovers within a few weeks or months and that was our experience in our only case. Cognitive effects, even with large resections, can be hard to detect but have been described. Likewise, providing that the remaining frontal lobe is healthy, the gross personality changes seen with frontal lobe disease do not occur. The lack of gross intellectual and psychiatric complications

from frontal lobe resections probably relies upon normal function in the remaining frontal lobe but may also be illusory in that the number of patients undergoing frontal lobe surgery is small and the patients are seldom submitted either preoperatively or postoperatively to intellectual or psychiatric tests of sufficient complexity to reveal deficits. Studies on our patients have revealed that they are impaired on an adaptation task [42] and perform poorly on the use of strategy [43] and on changing from one dimension to another [44].

Olivier [45], summarizing 108 frontal lobe resections in 1995, noted nine complications: three were non-neurological (2.8%), and there were two cases of postoperative oedema, three cases of transient dysphasia and one case of hemiparesis secondary to venous thrombosis (0.9%). In 2002, Schramm and colleagues [46] described 68 patients operated for frontal lobe epilepsy. All underwent lesionectomies, with added multiple subpial transection (MST) in 17 cases: there were 14 complications – three non-neurological complications (4.4%) and 11 cases of neurological deterioration or new deficits, which were temporary in 10 cases and permanent in one (1.5%).

Temporal lobe resection

Postoperative mortality is low; in recent series of mixed patients, children and the elderly, there was no surgical mortality [2,47–49]. In our own series there have been only two postoperative deaths in over 730 operations since 1976 (0.27%), and none since 1988. Other non-neurological complications are acceptably low and perhaps the commonest is postoperative infection, which is given at 0.5% in the Second Palm Desert Symposium [15]. Rare complications include distant haemorrhage in the cerebellum and lumbar spine, which were attributed to excessive CSF drainage [50–53], and a middle fossa cyst causing raised pressure [54]. Seizures are also described in the immediate postoperative period in about 20% of patients. If such seizures are similar to the preoperative ones then they are of poor prognostic significance, otherwise not [55].

Neurological sequelae

Neurological deficits after temporal lobe resections are acceptably low. Lesionectomy and neocortical removal are least likely to produce such problems so long as the superior temporal gyrus is respected. The sequelae of combined neocortical and deep removal and of selective mesial resections are similar.

Penfield *et al.* [56] first described hemiplegia following temporal lobectomy and attributed it to manipulation of branches of the middle cerebral artery [56]. The commonest neurological sequelae of temporal lobe resection are a contralateral hemiparesis or hemiplegia, a contralateral visual field defect and an homolateral third nerve palsy or paresis. Falconer and Wilson [57] showed that the relationship between the length of a temporal lobe resection and the subsequent visual field cut was due to the course of the visual fibres around the temporal horn. Such visual field defects relate to the disruption of the fibres in the roof of the temporal horn [58]. Katz *et al.* [59] showed that the more lateral the resection, the more likely it was to produce a deficit, although there was no close correlation between the size of the resection and the severity of the visual field defect [59]. The size of the defect cannot be predicted with resections of less than 7.5 cm. The extended lobectomy of Spencer *et al.* [60] does not produce more visual field defects than the standard operation. In our series, a complete field defect occurred in 12 operations among 440 (2.3%). A recent paper from Manji *et al.* [61] reports field defects in about 50% of 24 patients and with at least 24% failing the driving test criteria. This occurred in three patients who were seizure free.

The avoidance of hemiplegia or hemiparesis must be related mainly to vascular causes, especially in selective mesial resections, although the vascular injury is seldom apparent intraoperatively. In our series of temporal lobe resections the incidence was 2% in 400 operations, virtually all right sided. In temporal lobe resections the risk varies between 0 and 1–2% (being lower in larger series) and in selective amygdalohippocampectomy (SAH) varies between less than 0.5% in the Zurich series to 4% in our series.

A large series from Bonn notes a third nerve palsy in four patients (1.4%), a hemianopia in two patients and a hemiparesis in two patients (0.7%), with permanent neurological sequelae in five patients (1.8%) [2]. In a series of 89 paediatric cases reported from Bonn there were only two patients with permanent neurological sequelae, both hemipareses (2.2%): one arose from a haematoma after anterior temporal lobectomy, the other from arterial injury in the course of a SAH [47].

Intellectual sequelae

There are three basic questions to be considered. First, what is the influence of the presurgical condition of the patient on cognitive outcome? Second, what risks does the patient face of global amnesia after surgery? Third, is it possible to influence the cognitive outcome by variations in the operative technique?

It is known that patients with unilateral temporal lobe lesions have material-specific deficits and also that those patients with early onset of epilepsy have poorer cognitive performance preoperatively but also suffer less change in their performance as a consequence of the surgery [62,63]. Assessments of postoperative functioning must be seen against this background; most series of temporal lobectomy comprise varying numbers of patients of mixed aetiology.

The risks of global amnesia following temporal lobe resections were first reported in 1957 when it was realized that bilateral resection of the hippocampal structures led to profound and permanent amnesia [64]. It is not appropriate here to enter into a detailed discussion of the methodology for assessing preoperative memory reserve; suffice it to say that this may be a significant reason for refusing surgery. However, the patient undergoing unilateral temporal lobe surgery is still at risk of amnesia from two sources. The first is destruction of the remaining hippocampal complex from seizures, either acute or chronic. In 1992 one of our patients (operated on in 1991 and shown to have intact memory in postoperative assessment) had a prolonged generalized seizure after a weekend of heavy drinking resulting in severe amnesia. Similar cases have been reported from other centres [65–67]. The remaining temporal lobe, due to ageing, may suffer memory problems earlier [68].

There is considerable dispute as to the part played by the hippocampus and neocortex in memory. In addition, mesial temporal sclerosis is seldom purely unilateral and may exist as a primary pathology or in a milder form as a component of dual pathology.

In order to try to limit memory problems following surgery, more restricted operations have been introduced and variously described as 'tailored' or selective operations, of which the most prominent is the transsylvian SAH introduced by Yasargil and Wieser in 1985 [69]. It is generally accepted that the seizure outcome from these variations in temporal lobe resection is equal, provided that the pathology is the same and the removal is complete, and therefore it is the intellectual sequelae that are important. The surgical target may not be achieved as first described from Oxford in a comparison of transsylvian and transcortical amygdalohippocampectomy by the same surgeon. On MRI there was collateral damage, by which is meant unintentional damage to surrounding structures as a consequence of the surgical manoeuvres [70]. Jones-Gotman *et al*. [71] attempted to investigate the contribution of the various structures by examining patients operated in three centres with different techniques but was dogged by the same problem, resulting in the interesting conclusion that the effects on memory of temporal lobe resections were due to disconnection rather than ablation [71].

Wieser [72] notes that two factors influenced improvement: the first was when the non-operated side subserved the function and the second was freedom from seizures. Wieser [73] later suggested that right-sided operations result in an improvement in learning and memory, whereas left-sided operations have the converse effect. Katz *et al*. [59], using a method of quantitative analysis of postresection MR scans, attempted to correlate resection with intellectual changes. Decrease in verbal memory correlated with the extent of resection in the mesial and basal quadrants on the left, and a similar correlation was found with non-verbal memory and right-sided resections. In 1992 we studied 42 patients undergoing either amygdalohippocampectomy or temporal lobectomy, all of whom were left hemisphere dominant [74]. The side and type of operation were approximately equal. If seizures persisted then there was a poor performance in the material-specific tasks performed by the target temporal lobe. SAH had less effect on the functions of the target temporal lobe than anterior temporal lobectomy but the converse was true of the non-target temporal lobe. Jones-Gotman *et al*. [75] found few differences between the two techniques in her investigations. Two matched learning tasks, using abstract words versus abstract designs, were administered to patients with unilateral neocorticectomy, SAH or anterior temporal lobe resection invading the amygdala and hippocampus. Learning and recall for words were impaired in groups with resection from the left temporal lobe, irrespective of whether mediobasal structures were spared or temporal neocortex was spared. All right-resection groups were unimpaired. A recent publication from Bonn reflects our findings. Helmstaeder *et al*. [76] described 97 patients operated by SAH or temporal pole plus amygdalohippocampectomy. Verbal memory outcome was worse after left-sided operation, especially for SAH, whereas figural memory outcome was worse after right-sided operation, preferentially for temporal pole resection with amygdalohippocampectomy (TPR+) [76]. In a very detailed review, Schramm [77] concludes that the evidence (including papers from his own group) is mixed, but, on balance, and particularly in the long view (2–10 years after operation), selective operations have superior cognitive outcome. In conclusion, the cognitive advantages of SAH remain unclear.

Psychiatric consequences and social outcome

Behavioural changes after temporal lobe surgery are well documented but the patient usually benefits from the surgery. It has been long recognized that there is significant premorbid psychiatric morbidity in patients submitted to temporal lobe resections. In general, there is a reduction in psychiatric problems after surgery.

Psychosis supervening upon chronic epilepsy is usually a late event. Temporal lobe surgery, at any rate resective surgery, can produce a schizophreniform psychosis often associated with left-sided resections or a depressive illness more often associated with right-sided operations. In recent material the incidence of schizophreniform illness is low – in our series around 2–3%. The connection with left-handed females with alien tissue lesions described by Taylor and Bruton has not been generally confirmed, although Andermann *et al*. [78] reported similar findings in patients with ganglioglioma. Mace and Trimble [79] note that both left- and right-sided operations may be followed by psychosis. *De novo* postictal psychosis is described in 5.3% of 57 Finnish patients [80]. In a wider survey of patients with intractable epilepsy the most prevalent disorder was anxiety disorder (10.7%), a schizophreniform psychosis in only 4.3% [81]. Mayanagi *et al*. [82] described an incidence of 5% for postoperative psychosis in 100 patients who were subjected to temporal lobectomy. Two patients experienced increase of symptoms to full-blown obsessive–compulsive disorder after surgery [83] and Carran *et al*. [84] report mania in 16 patients out of 415 who underwent temporal lobectomy (3.8%).

A depressive illness presenting after temporal lobe surgery is more common, but does not necessarily occur *immediately* after surgery, and careful questioning may be required to elicit the symptoms. In our material, suicide is relatively rare (one known case in 400 operations) but depression is much more common – an informal survey suggests around 35%, mostly in non-dominant resections. We have found that it is rare after amygdalohippocampectomy and in children, although one 12-year-old child with a large resection developed clinical depression requiring treatment. Paradiso *et al*. [85] put the incidence of depression in their 70 patients at 34% and found that it was under-recognized and undertreated. Pintor *et al*. [86] noticed that a preoperative psychiatric history was commoner in patients who had postoperative psychiatric problems, although overall there was a clear reduction in depressive symptoms from 17.2% to 4.3% 1 year after surgery. Salzberg *et al*. [87] noted hypometabolism on an fluorodeoxyglucose (FDG)-PET scan in patients with depression.

Central and parietal resections

Any resection from the central area (i.e. the primary motor or sensory area) must carry some risk of loss of function, and this risk will be related to the pathology of the underlying disease process which may have already produced a disability or displaced the cortex away. It is now possible to identify the motor and sensory cortex in the context of both normal and abnormal cortices. The sophisticated use of structural MRI has also enabled surgeons to distinguish lesions that are distinct from cortex or displace it from those that involve cortex or may contain functioning tissue. The central cortex can now be identified reliably

on MRI and fMRI has become more accurate. It has been verified in comparison with transcranial magnetic stimulation [88], anatomical criteria [89] and the gold standard of mapping by stimulation during chronic intracranial recording [90] or directly at the surgery. Pinsker *et al*. [91] reported that the use of neuronavigation, cortical stimulation and repetitive neurological and language examinations reduces neurological deterioration from 33% to 12%.

Despite these precautions, unexpected deficits may occur. Although these could be due to wrong identification of the primary areas it may also occur if secondary vascular damage takes place because an artery or vein passing through a resected area is damaged, a mechanism postulated by Olivier and Awad [92]. They also note that the whole central area can be resected when there is no voluntary hand movement, position sense is absent and there is paresis of the lower limb. It is equally important to identify the postcentral gyrus to avoid profound proprioceptive loss in the hand or arm, which can be more disabling than pure motor loss. However, following the resection of discrete lesions there may be a transient deficit or no deficit. In a detailed review of 120 frontocentral resections the Paris group notes that 40% of patients were unchanged immediately after surgery and in 15.8% there was a minor defect, but in the remainder (44.2%) there was either a monoparesis or major hemiplegia. At 1 year or more after operation there was significant improvement with no change in 67.5%, a mild disability in 10% and an additional severe disability in 22.5% [93]. In a group of 57 patients there were eight patients in whom there was a discrete lesion; three of these underwent lesionectomy and the remaining five underwent corticectomy. There were mild deficits in only two of these patients [94]. Cascino *et al*. [95] reported similar findings describing one monoparesis among 14 patients who underwent stereotactic lesionectomy in the perirolandic region. In the dominant hemisphere, resections from the posterior temporal–parietal region run the risk of receptive aphasia, dyslexia, dysgraphia and dyscalculia. For this reason resections from these areas are usually avoided.

Occipital resections

Occipital resections form around 2–5% of most series. Preoperative visual field defects are present in 30–60% of patients [96] and visual field defects increase after surgery. Recently, Curatolo *et al*. [97] have reported the use of intraoperative photic driving to identify central visual cortex and describe two patients in whom they were able to preserve the central visual field. Bidzinksi *et al*. [98] also noted that a complete occipital resection always produced some visual field defect. However, two patients undergoing occipital lesionectomy described by Cascino *et al*. [95] had no defect. Williamson *et al*. [99] noted that most patients adapted to their visual field defect within 1 year of surgery.

Hypothalamic hamartoma

This lesion has come to prominence and there are a number of different approaches to it which partially depend upon the size and situation of the lesion. The pterional approach has now largely been abandoned as being ineffective. Other manoeuvres including stimulation, radiofrequency coagulation, etc. have their place but are little used. The main operations are the transcallosal approach, pioneered by Rosenfeld and Harvey [100], the resection and disconnection approach including endoscopic technique of Delalande and Fohlen [101] and stereotactic radiosurgery [101,102]. The transcallosal approach has been relatively free of complications. In 2004 Rosenfeld *et al*. reported results from 45 patients; morbidity was minimal, including transient hemiparesis in three, ongoing diabetes insipidus in two and early short-term memory impairment in 16 (persistent in six) [103]. A subsequent joint paper with the Barrow Institute describes persisting short-term memory impairment in 8–14% [104]. The Paris group used a combination of pterional microsurgical and endoscopic approach in 49 patients. Neurological complications occurred in two patients, in both cases with the pterional approach [105]. Regis *et al*. [106] has described the effect of gamma knife surgery on 27 patients, with improvements in cognition and behaviour, no permanent neurological complications and three cases of transient poikilothermia.

Major resections

These are defined as resections that involve more than one anatomical lobe. The creation of such a space within the cranial cavity does not in itself create any special problems, although the patients tend to be more constitutionally ill and cerebrally irritable postoperatively than those undergoing lesser resections. The creation or persistence of neurological deficits (especially limb dysfunction, such as hemiparesis or hemisensory loss, visual field defects or deterioration of speech function) is often related to the original pathology, which may have produced such defects in any event.

Hemispherectomy

Although hemispherectomy is a serious operation, it is likely that the mortality rate of 6–8% quoted at the Second Palm Desert Symposium [15] probably includes series of patients operated upon over a long period of time, and more recent series do not have such mortality. In a review of 333 patients by Holthausen *et al*. [107], perioperative mortality was 1.5%. In our own series of 53 operations there has been one immediate postoperative death (1.9%); Villemure and Daniel [108] quote 2.3% for functional hemispherectomy and Delalande *et al*. [109] 3.6% for hemispherotomy. Even series comprising infants now have a low mortality rate; for example there were no deaths among 18 patients aged under 24 months operated at the Cleveland Clinic [110].

It is impossible to discuss this topic without considering the various techniques available that are aimed at reducing serious side-effects and the underlying pathology that determines the extent of the additional damage inflicted by the surgery. In practice, these patients fall into three groups. First are those presenting with a major hemispheric insult (non-progressive) at a very early age. These patients usually have a complete infantile hemiplegia and average to low cognitive function. Their neurological status is usually unchanged by surgery and their cognitive function can be unchanged or improved [111]. The second group comprises those with Rasmussen's disease [112], in whom the hemiplegia may not be complete and there may be no visual field defect. Furthermore, because of the late onset, especially when the dominant hemisphere is involved, there may be irreversible cognitive changes that are worsened by the surgery [113]. Lastly, there is the group of patients with hemimegalencephaly in whom further

deterioration may occur but is less likely than with Rasmussen's disease.

Techniques have been changed to counter the difficulties of a major operation in infants and young children, and the problem of the large space created. In infants and young children blood loss may be sufficient to necessitate transfusion, even if the operation is conducted carefully. The worst problem is venous bleeding, which may be torrential and difficult to control in the short term. The position of the head has to compromise between too much elevation (which would risk air embolism) and too little (which would increase venous pressure, making haemostasis more difficult to secure). At present, most centres have changed from anatomical hemispherectomy or decortication to some form of disconnective hemispherotomy. There are a number of variants of hemispherectomy that were devised to overcome the well-documented consequences of anatomical hemispherectomy as described by Krynauw [114]. These complications of haemosiderosis and associated conditions occur even with modern techniques [115]. A possible solution is the *functional hemispherectomy*, which, in its most recent form, is the peri-insular operation proposed by Villemure and Mascott [116]. A more minimal operation, hemispherotomy, described in two separate forms by Delalande *et al*. [117] and Schramm *et al*. [118], also resolves this problem. These modified operations still have their complications. The exact frequency is difficult to discern because some series extend over a considerable period of time. Of interest is the report from Boston of 10 patients in whom blood loss, of proportions that required intensive care unit care to correct, was the main problem. In addition, haemorrhage into the operation cavity and seizures occurred [119]. A more recent report from Rome describes less severe complications, including anaemia in 12 out of 15 patients; a second surgical procedure was needed in eight patients, including five shunts, all in children operated on at less than 9 months of age [120]. In our own mixed series of 50 adults and children, only four required shunts and there were four cases of severe postoperative infection requiring removal of the bone flap. In two of these there had been exploration with large subdural grids. In terms of operating time and blood loss, at present some form of hemispherotomy or the peri-insular hemispherectomy is to be preferred. In Villemure and Daniel's 43 patients who were undergoing functional hemispherotomy there were two shunts and one haemorrhage [108]. In Delalande *et al*.'s 83 patients who underwent hemispherotomy there were 13 shunts [109]. Finally, Kestle and colleagues [121] made an interesting comparison between hemidecortication in five patients and peri-insular hemispherotomy in 11 patients. Those patients who underwent peri-insular hemispherotomy did better on all measures, such as blood loss, postoperative fever, ventriculoperitoneal shunt insertion and length of stay [121].

In conclusion, hemispherectomy and allied procedures now have acceptable mortality and morbidity rates but they do remain among the most dangerous, although the most effective, resective operations for drug-resistant epilepsy.

Reoperation

All surgeons are familiar with the technical difficulties of second or third operations at the same anatomical site. Awad and colleagues [122] were the first to outline specific difficulties of reoperation, and the matter has also been dealt with in detail by Germano *et al*. [123]. Awad *et al*. [122] noted that anatomical structures will frequently become distorted and MRI and neuronavigation are obvious aids to countering this problem. Vascular adhesions may form between the dura and cortex and these vessels may make a significant contribution to the blood supply of that cortex and therefore should be preserved as far as possible. Only one paper on reoperation, that by Salanova *et al*. [124] describing 39 patients who underwent reoperation in the frontal lobe, reports transient weakness in 28% and permanent neurological defects in 8% [124]. A further report on 41 patients reoperated in the temporal lobe had no morbidity [125]. Recent papers from other sources have similar results with no mortality and morbidity, chiefly increased visual field defects, at 10–15% [126,127].

Functional surgery

These procedures can be divided into three groups: interruption of fibre tracts (as in callosotomy and multiple subpial transection), stereotactic creation of lesions within the brain and stimulation of deep brain and other nervous system structures.

Callosal section

Complications from callosal section depend upon the extent of the section and the nature of the underlying disease process. When performed as an alternative to hemispherectomy in unilateral hemisphere disease it is clearly sensible to approach the midline from the damaged side. If these patients are of mixed cerebral dominance this may affect the side of the approach and the extent of the callosal section posteriorly.

The complications may be divided into acute and chronic and they are related to the extent of the resection, being minimal with a truncal section and greatest with an anterior two-thirds or total section. Venous ischaemia or even thrombosis, when unilateral, would manifest itself as a hemiparesis with the possible addition of focal seizures. There may be transient paresis, usually affecting one leg, due to retraction on the medial surface of the hemisphere. More serious, however, is the risk of akinetic mutism, probably the result of bilateral anterior cerebral artery spasm. Mortality in recent series was between 0 and 1.5% [128–130]. The Montreal Neurological Institute (MNI), reporting 43 operations, had no deaths, but there were some complications in 16 patients, including three patients with transient weakness of the right leg and four with decreased speech output, also transient [131]. Recent series have similar complication rates to earlier ones. Thus, in Nei *et al*.'s series of 87 patients [128] there were complications in 21%, and in Shimuzu's series of 76 patients there were four serious surgical complications (5%) [129]. In our own series of 28 patients who were undergoing anterior callosotomy, there has been one peroperative death from pneumonia and two patients developed acute anterior cerebral ischaemia, both of whom recovered completely. We have had transient limb weakness in a few patients and an extradural haematoma in one. In many series the complications are transient, as described by Maehara and Shimizu *et al*. [132] and Fandino-Franky *et al*. [133]. The former had 14 transient episodes of transient akinetic mutism in 59 cases (23.7%) and the latter had 10 cases of transient weakness and two of mutism in 95 cases (11.6%). Total callosal section has a higher risk of complications, and in a series of 76 patients reported by

Cukiert *et al*. [130] there were complications in 72 patients but all were resolved within 16 days. When callosotomy is carried out using stereotactic radiosurgery there appear to be fewer complications but there is the additional problem of delayed local oedema, common to all such treatments [134]. This invariably responds to steroid treatment. Therefore, in summary, the risk of death at callosotomy seems to be between 0% and 1.5% and the risk of permanent neurological deficit less than 5%, but the risk of transient deficit is up to 20%.

There are two important cognitive complications of callosal section. The first is changes in speech function in patients of mixed cerebral dominance for speech, in whom interhemispheric communication is essential for the proper comprehension and production of speech and related functions. This was first reported by Sass *et al*. [135]. It has been suggested, but is by no means the universal opinion, that a carotid amytal test to establish speech dominance should precede the surgery in every case and the operation, especially total section, should be refused to those of mixed dominance. The second potentially serious complication is the posterior disconnection syndrome. This is a situation in which complex motor or organizational tasks that require the combination of information from both hemispheres become impossible, as first described by Gordon *et al*. [136]. Sauerwein and Lassonde [137] noted that the cognitive effects of callosal section were related to the location and extent of the section as well as the age of the patient at the time of operation. Posterior section resulted in sensory disconnection; total callosotomy introduced problems with bimanual coordination and apraxia of the non-dominant hand to verbal commands. Many of these symptoms subside and those that remain are not disabling [137]. In 25 children, the effects of callosal section were less in younger children, and in older patients tended to resemble the pattern seen in adults [138].

Multiple subpial transection

Morrell *et al*. [139] devised this procedure for use in eloquent areas of cortex, attempting to produce good seizure control with minimal functional disturbance. Their experience is summarized in a review published in 1999. They report transient morbidity in the form of paresis and dysaesthesia lasting 2–3 weeks, although occasionally lasting some months. Permanent deficits were less common, occurring in only 14% of patients. In addition, there were unrelated complications in four other patients, bringing the overall complication rate to 19% [140]. In our own experience in 40 patients there have been severe complications in patients who underwent resection as well as MST; there were six hemipareses (30%) (four transient) and three hemipareses with MST alone (27% – two transient). In 2002, a comprehensive meta-analysis of cases from six centres was published. It was reported that when MST was used alone there were complications in 10 patients (19%), comprising four with memory decline, five hemipareses and one partial visual field defect. There was no persisting aphasia or sensory deficits after MST alone. Thirty-seven patients, however, had a persistent deficit after MST with resection [141].

Stereotactic lesions

The creation of lesions in apparently normal brain to control epilepsy by modification of brain activity has been proposed and performed for many years and by a number of methods. Generally speaking, they were directed to temporal and extratemporal targets. However, these procedures are now not much used.

There are reports on the use of stereotactic radiosurgery in treating drug-resistant epilepsy due to mesial temporal sclerosis and hypothalamic hamartoma. The number of patients reported is small but there do not appear to be any of the particular complications of radiotherapy, such as radiation necrosis. In two recent reports the Marseille group reported only minor complications in 15 patients with mesial temporal sclerosis who were followed up for more than 2 years. Four patients had transient worsening of seizure activity and eight patients had cephalgia [142]. In this paper two patients were described as having a significant field defect and in another paper nine patients had field defects, eight of whom were asymptomatic and the remaining one was hemianopic [143].

Stimulation

Clearly, the use of chronic indwelling stimulating electrodes will run the risk of complications that are commonly associated with such apparatus. These must include implant failure and infection. These are relatively rare and occur with the same frequency as any other implanted device. When the stimulating electrodes are intracranial there is also the possibility of CSF leakage.

At present the only stimulation procedure in common use in epilepsy is stimulation of the left vagus nerve. The complications associated with this procedure fall into three groups.

The surgical complications include haematomas in the generator pouch, which occur rarely and are usually treated conservatively. They are likely to be less common as the devices become smaller. Infection occurs at a steady rate, which is low. Ben Menachem and French [144] quote 3–6%, and this is probably correct, although infection serious enough to need explantation is lower. There are alternatives to explantation, as suggested by Ortler *et al*. [145]. Similar figures have been quoted in recent papers describing series of children [145–47]. Hardware failures are rare, occurring in perhaps less than 1% of cases. Paralysis of the left vocal cord, probably as a result of excessive nerve manipulation, is also seen, in probably less than 5% of cases, and usually resolves with time. In early series there were reports of a Horner's syndrome, which is due to extending the dissection too deeply [148]. There is a substantial literature on the effects of vagus nerve stimulation on laryngeal function. Apart from the more permanent effects, which are rarely observed, as already explained, effects that are normally well tolerated may, in the case of excessive stimulation, result in adductor spasm [149].

There was anxiety about cardiac and respiratory effects of intermittent vagus nerve stimulation, as bradycardia and asystole have been reported during lead testing at implantation. However, this is rare (in Ardesh's recent report 2.7%, and in our series less than 1%) and now is generally not seen as a reason for explantation or not using the device [150,151). Patients undergoing a general anaesthetic for some other reason should have the device turned off. There have been rare deaths from pneumonia but studies have not shown that vagus nerve stimulation causes aspiration [152,153]. In our series of over 120 implantations there has been one death and one serious morbidity from pneumonia in the postoperative period, unrelated to aspiration. Lotvall and colleagues [154] have described deterioration in lung function in

patients with chronic obstructive airways disease. Malow *et al.* [155] have shown adverse changes in respiration during stimulation when the patient is asleep and note that it is more significant in patients with obstructive airways disease.

There are also the problems associated with the intermittent stimulus. These were thoroughly explored in the trials and are described by Ben Menachem and French [144]. They include voice change (usually hoarseness), coughing and, occasionally, shortness of breath. Many of these effects are related to the amplitude of stimulation and tend to become less obtrusive with time and at a constant level of stimulation. Typical figures are those given by Morris and Mueller [156], with hoarseness at 28% and paraesthesiae at 12% at 1 year, hoarseness at 19% and headache at 4.5% at 2 years, and shortness of breath at 3.2% at 3 years. Vagus nerve stimulation and callosotomy have been compared and it is evident that the complications from vagus nerve stimulation are less frequent and much less serious than those from callosotomy [128].

Deep brain stimulation for epilepsy has been directed at two targets: the cerebellum and the thalamic nuclei. Cerebellar stimulation was introduced by Cooper *et al.* [157] but subsequently shown to be ineffectual [158]. Complications were rare; there were anecdotal reports of sudden death but these occur in epilepsy anyway. Deep brain stimulation has also been applied to the thalamic nuclei and to the subthalamic nucleus. Studies are sparse and inconclusive. The same potential complications must exist as with stereotactic lesioning, mainly malposition of the electrodes and haemorrhage.

Risk management

In the surgical management of chronic drug-resistant epilepsy, the use of interventional procedures in presurgical evaluation, and the therapeutic procedures themselves, can never be without risk of significant physical, intellectual and psychiatric complications. The impact of these complications spreads beyond the patient and surgeon to the family, referring physician, referring organization and society itself.

Because most epilepsy surgery or invasive diagnostic procedures are a matter of choice rather than involving decisions made under pressure of clinical circumstances, the concept and application of informed consent is especially important. A person taking such consent must be sufficiently senior and experienced to make them competent for that task and the person giving it must have understood the explanation and implications. It may be impossible to achieve this in one session. It is especially important that any such discussion should include the particular experience or facilities of the group undertaking the procedure, as these will influence the possible frequency and severity of complications. It is not clear what legal validity the present operation consent form used in the UK has. It is commonsense to make sure that it is countersigned by the operating surgeon or equivalent. A written record that a discussion regarding the purpose of the procedure and possible complications has taken place should exist and, if appropriate, the actual complications should be listed. In the Sidaway case it was hoped that an objective frequency of any complication would be suggested, above which the patient must be warned. However, after appeal to the House of Lords it was stated that the surgeon must warn only of those complications that a reasonable body of professional practitioners would warn the patient of, and that, in the UK at any rate, is where the matter stands [159]. This is in keeping with the Bolam test, which uses the proposition that a practitioner cannot be accused of negligence if he/she acts in accordance with practice accepted at the time by a responsible body of medical opinion [160].

Conclusion

- The complications of epilepsy surgery must include the complications from invasive procedures used in presurgical assessment, as well as those arising in relation to therapeutic interventions.
- The intracarotid sodium amytal test has a low complication rate, less than 0.5%, in the classical form.
- Intracranial electrodes have a complication rate that increases with the invasiveness and complexity of the procedure. Mortality is zero, but there is a significant complication rate from haemorrhage and infection of 2–5%.
- Therapeutic procedures are divided into resective and functional operations. Overall perioperative mortality in large series of mixed procedures is 1% and overall mortality, including late deaths, is around 2–3%.
- In resective surgery morbidity depends upon the size and site of the resection. It can be very low in non-eloquent areas such as the non-dominant frontal lobe: around 1% compared with greater than 30% in central and occipital regions.
- In unilateral hemisphere disease the age of the patient, the underlying pathology and the operative technique used will all affect the nature and severity of the potential complications.
- In temporal lobe resections there are additional intellectual and behavioural consequences of the procedure, dependent upon the preoperative status of the patient and the nature of the resection.
- Reoperation and functional procedures such as callosotomy and multiple subpial transection also carry significant risk.
- Risk management is also important.

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80 Anaesthesia for Epilepsy Surgery

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Preanaesthetic evaluation for epilepsy surgery

Anaesthesia for epilepsy surgery, perhaps more than anaesthesia for any other neurosurgical procedure, requires the anaesthesia team be extremely well informed about the specifics of the condition that necessitates the surgery. Thus, it is the author's practice to have the following questions in mind when conducting the preoperative evaluation of a patient with a chronic seizure disorder scheduled for epilepsy surgery: What is the seizure type and frequency? Does the patient experience a warning symptom or aura? What circumstances, if any, precipitate seizures? What are the ictal manifestations and postictal behaviours? What antiepileptic drugs (AEDs) is the patient taking? Is there a history of any adverse reaction to previously used AEDs? If the seizures are part of a syndrome, how might that syndrome also affect anaesthesia management?

The preoperative assessment should address the potential toxicities of AEDs, such as bone marrow suppression, anaemia, thrombocytopenia, liver toxicity, and electrolyte and acid–base abnormalities. If not identified preoperatively, common side-effects of anticonvulsant therapy might cause perioperative adverse events or, at a minimum, diagnostic dilemmas. For example, patients on topiramate (Topamax) may have markedly low serum bicarbonate levels due to carbonic anhydrase inhibition and increased renal bicarbonate losses [1,2]. The benefit of awareness of a pre-existing acidosis that might be worsened by intraoperative conditions, such as administration of normal saline, hypoventilation and volume depletion, is clear. A similar benefit would be gained from knowledge of hyponatraemia associated with oxcarbazepine and carbamazepine therapy. This side-effect, attributed to altered sensitivity of hypothalamic osmoreceptors, or increased sensitivity of renal tubules to antidiuretic hormone, is usually subclinical but cases of clinically significant hyponatraemia are reported [2–4]. In the absence of clinical symptoms or signs of hepatotoxicity, routine preoperative liver function tests are not indicated. However, mild asymptomatic biochemical abnormalities in liver function are not infrequent during therapy with AEDs that induce liver enzymes (e.g. phenobarbital, carbemazepine, phenytoin) [5]. If discovered, these are not considered a contraindication to anaesthesia and surgery [6]. Finally, blood levels of AEDs should be reviewed to guide decisions about perioperative drug administration.

Prior to anaesthesia for procedures that do not involve intraoperative or perioperative analysis of epileptiform activity, it is appropriate to continue the preoperative antiepileptic drug regimen, whereas before anaesthesia for procedures that involve intraoperative analysis of epileptiform activity, it is best to plan perianaesthetic AED administration in consultation with the neurology and neurosurgical teams. An exception to this general rule is perioperative administration of valproic acid. In some practices valproic acid therapy is continued perioperatively, whereas in others the drug is discontinued before elective neurosurgery. The rationale for stopping valproic acid therapy preoperatively is that it has been shown to affect platelet function and clotting factors, although whether these effects are related to a specific dose range, idiosyncratic or predictable, is not clarified [7]. The rationale for continuing valproic acid is that, although some reports have attributed intraoperative and postoperative hemorrhagic complications to valproic acid, several studies failed to demonstrate any increase in haemorrhagic complications in patients undergoing neurosurgery while taking valproic acid [8,9]. Resolution of this controversy awaits a greater understanding of the effect of valproic acid on haemostasis. Valproic acid is also known to cause dose-dependent thrombocytopenia, which, in any case, would need to be addressed before elective epilepsy surgery [10].

Anaesthesia and antiepileptic therapy

In the past several decades the armamentarium of AEDs has substantially expanded. In addition to the 'classic' and still widely used valproic acid, phenytoin, phenobarbital and carbamazepine, neurologists treating seizure disorders can choose among newer AEDs including felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), levetiracetam (Keppra), oxcarbazine (Trileptal) and zonisamide (Zonegran). Although some of these drugs are significantly protein bound and several cause mild induction of liver enzymes, clinical experience and limited reports from the literature suggest that interactions of these new AEDs with agents used during anaesthesia are generally of minor clinical significance. In contrast, there is substantial information about the interactions of 'classic' AEDs, for example valproic acid, phenytoin, phenobarbital and carbemazepine. These drugs have significant interactions that alter patient response to agents used during anaesthesia.

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Patients receiving chronic anticonvulsant therapy with 'classic' AEDs require increased maintenance doses of fentanyl during balanced anaesthesia for craniotomy [11]. It is not known whether this finding is explained by enhanced fentanyl metabolism or an effect of chronic anticonvulsant medications on opiate receptors. Another clinically relevant interaction with narcotic medication is the induction of hepatic enzymes by chronic administration of phenobarbital causing increased N-demethylation of pethidine to the neurotoxic metabolite norpethidine [12].

After prolonged treatment with 'classic' AEDs, patients may require larger and more frequent doses of neuromuscular blocking drugs to maintain muscle relaxation during surgery because the recovery time of non-depolarizing neuromuscular blockers is markedly reduced. On occasion, the reduction in recovery time is so profound that paralysis due to neuromuscular blocking agents given to facilitate endotracheal intubation has dissipated by the time of head positioning for neurosurgery a short time later. Frequent or continuous monitoring of neuromuscular blockade is advisable to prevent untoward events that are likely to provoke patient movement in these and other circumstances.

Patients who are chronically treated with phenytoin or carbamazepine are resistant to the steroidal muscle relaxants pancuronium, vecuronium and rocuronium [13–16]. These interactions are probably multifactorial, involving altered protein binding, decreased receptor sensitivity and increased numbers of cholinergic receptors, as well as increased metabolism. In contrast, recovery from atracurium, a benzylisoquinolinium class drug, is not affected by chronic administration of phenytoin or carbemazepine [17,18]. However, recovery from cisatracurium, another benzylisoquinoline-derived agent, is faster in patients on chronic phenytoin and carbamazepine, although the magnitude of the effect is smaller than that observed when steroidal non-depolarizing neuromuscular blocking drugs are administered [19].

The anaesthesia team is often asked to administer AEDs intraoperatively, either to augment subtherapeutic blood levels or to provide postoperative seizure prophylaxis for patients on AEDs that cannot be administered intravenously. The most common adverse effect of AEDs that are administered intraoperatively is undoubtedly hypotension during phenytoin administration. Under anaesthesia, and in non-emergent situations, it is wise to administer phenytoin substantially more slowly than the recommended maximum infusion rate of 50 mg/min in adults and 1–3 mg/min in children and neonates. Additive sedation is another potential side-effect of intraoperatively administered anticonvulsants, particularly when phenobarbital is given. Finally, as anticonvulsants are frequently infused towards the end of surgery, it is worthwhile noting that acute phenytoin administration to patients who are not chronically receiving the drug results in augmentation of the existing neuromuscular blockade [20].

Under anaesthesia, gastrointestinal absorption of AEDs is unreliable and might result in inadequate blood levels. Some AEDs have parenteral formulations (phenytoin, valproate, levetiracetam, phenobarbital) that can be substituted for oral medications during the perioperative period. Alternative therapies must be considered if oral administration of medications that do not have a parenteral formulation, for example carbamazepine, will not be resumed in a timely fashion.

The ketogenic diet, prescribed for patients with seizures refractory to medical management, is another therapy that influences anaesthetic management. Postulated mechanisms for the anticonvulsant effect of the diet include improved cerebral energy stores and ketone body-mediated enhancement of chloride conductance at glycinergic and GABAergic synapses [21]. As the diet is more frequently encountered during anaesthetic management of children, the perioperative considerations are included in a later section of this chapter that addresses anaesthesia considerations for epilepsy surgery in children.

Anticonvulsant and proconvulsant properties of anaesthetics

Many drugs used in anaesthesia have proconvulsant or anticonvulsant effects. The literature on this topic is extensive but ambiguous. One source of ambiguity is the doubtful standard of 'movement consistent with convulsive activity during anaesthesia' applied in some reports that lack electroencephalography corroboration to define drugs that are administered during anaesthesia as epileptogenic. Another source of ambiguity is the tendency to extrapolate observations from non-epileptic subjects to patients with chronic intractable epilepsy and vice versa. In fact, different responses to anaesthetic drugs are observed even among populations of patients with different types of epilepsy. To add to this complexity, some drugs used in anaesthesia have proconvulsant and anticonvulsant effects at different doses, some have proconvulsant metabolites and some used to activate seizure foci during epilepsy surgery have also been used to treat status epilepticus. To provide the reader with some general guidelines for the use of anaesthesia drugs during epilepsy surgery, the following discussion summarizes pertinent information from several comprehensive reviews [6,22,23].

Intravenous anaesthetic induction drugs have proconvulsant and anticonvulsant properties. The barbiturate induction drugs thiopental and methohexital have anticonvulsant properties and can be used to treat status epilepticus. On the other hand, methohexital administered in hypnotic doses can precipitate seizures in patient with epilepsy and low-dose methohexital (<0.5 mg/kg) can activate seizure foci in patients with temporal lobe epilepsy, a property that has been used to define seizure foci intraoperatively. Low-dose thiopental can also activate seizure foci in patients with epilepsy but is less effective than methohexital for this purpose [24].

Propofol has anticonvulsant properties in experimental animal models, decreases the duration of seizure activity in patients undergoing electroconvulsive therapy and has been used to treat status epilepticus resistant to other forms of therapy [25]. Infusion of propofol diminishes epileptiform activity in epileptic patients who are undergoing intraoperative electrocorticography. Nevertheless, there are reports of electroencephalography-documented seizure activity in patients after administration of propofol. This phenomenon is observed at lower plasma concentrations and disappears when drug levels are augmented.

Ketamine is proconvulsant in experimental animal models, activates seizure foci in patients with epilepsy and is generally considered to be contraindicated in patients with epilepsy.

Etomidate also activates seizure foci in patients with epilepsy [26]. Both agents have been used to treat status epilepticus. In summary, most of the intravenous induction agents have proconvulsant and anticonvulsant effects or both. Taken together, the information available suggests that methohexital, etomidate and ketamine are unlikely first-choice induction drugs for epileptic patients.

Inhalation agents also have proconvulsant and anticonvulsant properties. The proconvulsant effects of enflurane, an agent not in common use today, especially at high alveolar concentration [1.5–2 minimum alveolar concentration (MAC)] and during hypocarbia, are well known [27]. This consideration, among others, influenced anaesthesiologists to abandon the use of enflurane for neurosurgical anaesthesia when isoflurane was introduced into clinical practice. Isoflurane, despite occasional reports of seizure-like activity occurring during its use, has anticonvulsant properties at commonly used alveolar concentrations and has been used to treat status epilepticus.

Sevoflurane and desflurane are now the inhalation agents most commonly used in the clinical practice of anaesthesiology. Limited information suggests that desflurane is not epileptogenic, even at high alveolar concentration or during hypocapnia. In contrast, studies demonstrate that sevoflurane administration is associated with epileptiform electroencephalographic activity in epileptic and non-epileptic patients [28–32]. This association appears to be dose dependent, with a threshold at 1.5–2 MAC. Proposed risk factors in non-epileptic patients include rapid induction, high alveolar concentration, hyperventilation and female sex [33]. No patient studied to date has suffered any apparent consequence of the epileptiform activity recorded. The information available regarding the epileptogenic potential of sevoflurane has led to the recommendation that the maintenance concentration of sevoflurane be limited to 1.5 MAC [34].

High potency μ-receptor agonists are proconvulsant in animals. High-dose fentanyl and sufentanil induce epileptiform activity in non-epileptic patients who are undergoing cardiac surgery, and in patients with complex partial epilepsy rapid intravenous administration of large doses of fentanyl, alfentanil and remifentanil is epileptogenic [35–37]. The mechanisms postulated to mediate the proconvulsant actions of opioids include interactions with limbic opioid receptors, release of excitatory amino acids and suppression of inhibitory interneurones. A disinhibition mechanism is the hypothesis that is given the most credence, based on available data [36,38].

Anaesthesia and electrocorticography

Electrocorticography is used to define the location of cortical epileptogenic foci, to delineate the limits of therapeutic cortical resection and to confirm complete surgical removal of epileptogenic foci. It involves detection of characteristic interictal electroencephalogram (EEG) abnormalities via grids of electrodes placed over the surface of the brain. Placement of these grids requires a craniotomy. Depending on the circumstance, electrocorticography after grid placement may be performed intraoperatively under general anaesthesia, intraoperatively during so-called 'awake' craniotomy or extraoperatively awake.

Given the anticonvulsant effects of many anaesthetic agents, it goes without saying that if electrocorticography is to be performed in sedated patients or under general anaesthesia the anaesthetic technique must be tailored to provide optimal conditions. Exactly how that should be accomplished is quite a bit more controversial and neither the best anaesthetic for electrocorticography during craniotomy with awake intraoperative brain mapping nor the best anaesthetic for electrocorticography under general anaesthesia, which some consider an oxymoron, has been precisely defined. That said, many agents used during anaesthesia can suppress the interictal spike discharges that are used to identify epileptogenic tissue.

Several drugs used for anxiolysis during anaesthetic management are anticonvulsants at sedative doses and can inhibit interictal epileptiform activity. Avoiding benzodiazepine premedications in advance of procedures involving electrocorticography is widely recommended. Propofol infusion also can suppress interictal spike discharges at sedative doses but the duration of this effect is relatively short and several studies have found adequate conditions for diagnostic electrocorticography when propofol infusion is suspended for 15–30 min in advance of awake intraoperative electocorticography [39,40]. On the other hand, satisfactory conditions for electrocorticography are reported in patients who are administered dexmedetomidine by infusion for sedation [41,42]. Similarly sedative doses of remifentanil (0.1 μg/kg/min) are reported to provide adequate conditions for monitoring epileptiform activity during epilepsy surgery [43].

General inhalation anaesthesia is often administered for epilepsy surgery that does not require awake functional brain mapping. Under certain conditions, all inhalation anaesthetics may decrease interictal epileptiform activity. Isoflurane is reported to decrease interictal spike frequency at 0.5–1.5% [44]. Although at high alveolar concentrations sevoflurane can activate epileptiform activity in patients with intractable epilepsy, even in areas not confined to the ictal zone [28,31,32,45], during fentanyl-based anaesthesia sevoflurane decreases epileptiform activity at 0.5–1.5 MAC [46]. Nitrous oxide also decreases interictal epileptiform activity on electrocorticography in patients with epilepsy [47].

It is the practice at our institution, and many other centres as well, to discontinue potent inhalation agents in advance of electrocorticography and to maintain anaesthesia during recording with a combination of narcotic and nitrous oxide. If this anaesthetic is planned it may be reasonable to inform patients of an increased, although still extremely small, risk of recall during the period of electrocorticography, to explain the rationale for the modification of the anaesthetic technique during mapping of the seizure focus, and to provide reassurance regarding the likelihood of experiencing pain. Other 'light' general anaesthetic techniques and neuroleptanalgesia protocols designed to accommodate electrocorticography during epilepsy surgery are described but these have not been systematically evaluated.

Another widely used approach to delineating seizure foci during general anaesthesia is to administer medications that trigger epileptiform activity. Bolus administration of fentanyl (10 μg/kg), alfentanil (30–50 μg/kg) and remifentanil (1–2.5 μg/kg) induces epileptiform activity in patients with complex partial epilepsy [36–38]. A proposed advantage of remifentanil for this purpose,

compared with other opioid options, is that remifentanil has a short duration, even after a large dose, and, thus, its administration would be unlikely to contribute to postoperative sedation that could hinder early postoperative neurological evaluation. Subhypnotic doses of methohexital (0.3–0.5 mg/kg) and etomidate (0.05–0.1 mg/kg) have also been used to activate seizure foci intraoperatively [24,26]. An enduring debate is whether these triggering agents might mislead by activating epileptiform activity outside the ictal onset zone.

Anaesthesia for presurgical diagnostic tests

Patients undergo a wide variety of tests during the preoperative evaluation for the surgical treatment of epilepsy. These include: brain imaging studies, such as computed tomography, magnetic resonance imaging and positron emission tests; neuropsychological testing to determine hemispheric dominance such as the Wada test; and electroencephalographic evaluation via telemetry, depth electrodes and subdural grids. Some of these procedures are routinely performed under general anaesthesia, some can be performed with general anaesthesia or sedation, and some are performed with anaesthesia only if the patient cannot tolerate the test awake.

Placement of subdural grid electrodes requires a craniotomy and is performed under general anaesthesia. As electrocorticography for seizure focus mapping is performed after the operation there is no limitation on use of anaesthetic agents that suppress epileptiform activity. Venous access should be sufficient to accommodate the rare instances when grid placement breaches an afferent to the sagittal sinus with significant ensuing blood loss.

Placement of depth electrodes is performed under local or general anaesthesia according to institutional preference and patient requirements. Before the patient comes to the operating theatre, a stereotactic frame is placed and an MR scan is obtained with the frame in place. The frame limits neck mobility and, depending on the patient's particular physical characteristics, may also interfere with access to the airway. Thus, careful assessment is needed to plan for intraoperative airway management. Awake fibreoptic endoscopy-assisted endotracheal intubation is one solution but other approaches – the laryngeal mask airway, the intubating laryngeal mask airway and the glide scope – have been used successfully. Of course, whenever any drug with the potential to depress respiration is administered to a patient in a stereotactic frame, the immediate availability of equipment required to remove the frame should be confirmed. Hyperventilation during depth electrode placement can theoretically alter the position of intracranial structures targeted during an MR scan obtained while the patient is breathing spontaneously. Although a very rare event, emergency craniotomy may become necessary in the event of intracranial haemorrhage due to electrode placement. Removal of depth electrodes can usually be performed with intravenous sedation.

Other presurgical evaluations, such as the Wada test, which evaluates language and memory after unilateral hemispheric inactivation by a short-acting hypnotic injected into the carotid artery, functional magnetic resonance imaging, magnetoencephalography and positron emission tomography, are usually performed without anaesthesia except in children and uncooperative adults. Sedation with propofol at doses required to provide immobility may not alter the likelihood of recording interictal epileptiform activity during magnetoencephalography [48] or compromise neuropsychological testing if used for the angiographic portion of the Wada test [49].

General anaesthesia for epilepsy surgery

Focal cortical resection and temporal lobectomy are often performed under general anaesthesia in patients who do not require awake intraoperative mapping for delineation of functional cortex in close proximity to the proposed cortical resection. If intraoperative electrocorticography is planned then premedication with benzodiazepines is inadvisable. Very anxious patients may benefit from premedication with narcotics or propofol, with appropriate monitoring, in the preoperative area. Propofol is also a suitable intravenous hypnotic for induction of anaesthesia. A history of a seizure disorder does not influence the selection of neuromuscular blocker to facilitate intubation although, as noted, the duration of action of aminosteroidal non-depolarizing neuromuscular blockers is greatly reduced by several widely used antiepileptic medications. In common with other intracranial neurosurgical procedures, the goals of general anaesthesia for epilepsy surgery are analgesia, amnesia, stable haemodynamics, optimal operating conditions and early emergence for neurological evaluation. Total intravenous anaesthesia, balanced anaesthesia and inhalation anaesthesia can be used to achieve these goals. Anaesthetic technique may need to be modified to accommodate electrocorticography. Decisions regarding ventilation should take into account the possibility of precipitating seizure activity by hyperventilation. Other effective means to achieve optimal surgical conditions are administration of mannitol and positioning of the patient to optimize cerebral venous drainage. Normovolaemia is maintained by administration of isotonic crystalloid. Significant blood loss is rare. Clinical experience suggests that brief transient decreases in heart rate, which normalize when surgical manipulation is discontinued and rarely require treatment, are common during temporal lobectomy in patients with intractable epilepsy. A report of six cases of severe bradycardia in a series of 42 consecutive patients who were undergoing temporal lobectomy supports this clinical observation. All of the episodes of bradycardia in the reported series occurred during amygdalohippocampectomy. The authors suggest that this phenomenon may be related to stimulation of the limbic system, which, in experimental settings, increases parasympathetic outflow [50].

Anaesthesia for awake intraoperative brain mapping

In some centres, in appropriately selected patients, electrocorticography is routinely performed at the time of craniotomy for lesion resection, with the patient awake for an interval of time during the surgical procedure. In other centres, patients undergo awake intraoperative mapping during epilepsy surgery only if the seizure focus is located adjacent to eloquent brain areas, particularly language areas. And, finally, in some centres cortical mapping is always performed extraoperatively after subdural grids are placed during a craniotomy under general anaesthesia.

Awake intraoperative electrocorticography and functional brain mapping present a unique set of challenges for the patient and the anaesthesiologist. Optimally, the patient is sedated or unconscious, ventilating adequately, haemodynamically stable and immobile during the craniotomy, awake and cooperative for mapping procedures, and then again sedated or unconscious, ventilating adequately, haemodynamically stable and immobile during closure of the craniotomy. Several techniques have been used to accomplish these general goals. Appropriate patient selection, careful patient preparation and excellent teamwork are also important.

Most patients scheduled for epilepsy surgery with awake intraoperative brain mapping are highly motivated. Nevertheless, the anaesthesiologist can do much to allay anxiety about the procedure. Patients should be prepared by frank discussion of what they can expect to experience. The preoperative evaluation should further identify conditions that may increase the risk of the procedure such as morbid obesity, obstructive sleep apnoea, difficult airway and gastroesophageal reflux disease. It is a good idea to have a clear idea of the patient's seizure history and to anticipate any postictal behaviours (such as confusion, abnormal mentation, aggression or vomiting) that might be problematic if they occur with an open craniotomy in a patient with an unsecured airway. Other than inability to cooperate, there are few absolute contraindications to craniotomy with awake intraoperative brain mapping.

All anaesthetic techniques for craniotomy with awake intraoperative brain mapping rely on regional anaesthesia provided by infiltration of long-acting local anaesthetics. Scalp block can be performed by blocking cutaneous nerves at discrete locations, which requires a lower volume of local anaesthetic, or by regional infiltration. Scalp block performed with bupivicaine and epinephrine is effective for 8–12 h. As the scalp is highly vascular, systemic absorption of local anaesthetic is rapid. Plasma levels peak 5–10 min after administration of bupivicaine with epinephrine. Bupivicaine has a long track record in this setting, but the newer long-acting agents levobupivicaine and ropivicaine offer the theoretical benefit of lower potential cardiac toxicity [51,52]. In reviews of complications encountered during awake craniotomy in patients with seizure disorders, local anaesthetic toxicity is an infrequent event.

Craniotomy with awake intraoperative brain mapping has been performed with local anaesthesia alone. However, most patients benefit from some degree of sedation during the stimulating parts of the procedure, which include injection of the local anaesthetic, drilling, bone work and traction on the dura. Anaesthetic techniques vary according to the target level of consciousness, the agents used and airway management. Although anaesthesia techniques that involve sedation and analgesia are widely used, some centres have transitioned to 'asleep–awake–asleep' anaesthesia techniques that provide general anaesthesia for the craniotomy and closure. During the 'asleep' parts of the procedure, three airway management approaches are used: spontaneous ventilation with no intervention (except possibly a nasal trumpet), ventilation maintained via laryngeal mask airway and endotracheal intubation with controlled ventilation.

At the author's institution, for the last decade, we have used an asleep–awake–asleep technique with endotracheal intubation. First reported in 1998, we have now used this technique, or a modification of it, which incorporates routine use of a tube changer, in more than 150 patients [53]. After induction of general anaesthesia, nasotracheal intubation is performed with a commercially manufactured endotracheal tube that allows for intratracheal installation of local anaesthesia. Anaesthesia is maintained with inhalation agents or intravenous anaesthesia during positioning, scalp block, placement of the pin head holder and craniotomy. Hypnotic and analgesic agents are then either discontinued or administered at low dose until the patient is ventilating adequately and responsive, at which point the endotracheal tube is removed over a tube changer. After awake intraoperative mapping is completed, the endotracheal tube is reinserted over the tube changer. This technique provides for maximal patient comfort and a secure airway during the craniotomy, a means of reliable hyperventilation and a means to rapidly secure the airway. Further analysis of our case series is required to fully evaluate and compare this technique with other airway management protocols.

The ideal drug for craniotomy with awake intraoperative brain mapping is sedative, hypnotic, analgesic, amnestic, anxiolytic, easily titratable, rapidly reversible, antiemetic, compatible with electrocorticography, and causes minimal respiratory depression. Although deviating in several respects from these ideal characteristics, propofol and remifentanil do have pharmacological profiles that are particularly suited to rapid adjustment of levels of sedation and analgesia and, both singly and in combination, they are widely used for sedation/analgesia and general anaesthesia for these cases. Although propofol should be discontinued, remifentanil can be continued at sedative doses during electrocorticography without concern for suppression of epileptiform activity. Rapid intraoperative wake-up times prior to brain mapping procedures have been reported with propofol [54] and with remifentanil and propofol in combination [55,56]. Propofol and remifentanil administration, guided by pharmacokinetic simulation and bispectral index monitoring, is also reported to provide for rapid transition from general anaesthesia to a level of consciousness suitable for intraoperative neurological testing [56].

Dexmedetomidine, the latest addition to the armamentarium of sedative drugs used in this setting, has the advantage of producing sedation and anxiolysis without respiratory depression. It has been reported to be useful for craniotomy with awake intraoperative brain mapping as a component of sedation analgesia, as an adjunct during asleep–awake–asleep anaesthesia, and as a rescue drug for patients who, because of anxiety or dysphoria, are no longer able to tolerate being awake before intraoperative testing is completed [41,57–59]. Dramatically suboptimal conditions for neurocognitive testing during arteriovenous malformation embolization with dexmedetomidine sedation have described. In contrast, several reports describe excellent conditions for intraoperative neurocognitive testing with dexmedetomidine sedation during craniotomy [57,60]. The experience to date suggests that the lower range of dexmedetomidine dosing is less likely to result in poor conditions for intraoperative awake brain mapping.

Reliable and rapid emergence for awake intraoperative testing has been accomplished with a wide variety of anaesthetic techniques, including neuroleptanalgesia, combinations of short-acting hypnotics and narcotics, and inhalation anaesthesia. In fact, several studies comparing techniques reveal that practice

modification often diminishes the clinical consequence of drug selection and that the challenges related to drug side-effects decrease as experience is gained [61,62]. Nevertheless, some important differences between techniques have been discerned. For example, in a comparison of neuroleptanalgesia and propofol for sedation during awake craniotomy for epilepsy surgery the incidence of seizures was significantly lower in the propofol group [63].

Although the incidence of major complications is low, in order to provide the safest possible anaesthetic the anaesthesiologist has to be prepared for adverse events that are anticipatable during craniotomy for epilepsy surgery with awake intraoperative brain mapping. These include seizures, nausea and vomiting, hypoventilation, apnoea, hypercarbia, claustrophobia, dysphoria, agitation, pain, inadequate brain conditions and excessive sedation [64,65].

Most seizures are precipitated by cortical stimulation procedures, are short lived, of minimal consequence, and do not require therapy. Occasionally, intravenous hypnotics or benzodiazepines are required to terminate longer seizures. From time to time postictal depression will confound functional testing. Rarely, seizure-associated brain swelling and/or motor manifestations will require emergent conversion to general anaesthesia with controlled ventilation.

Nausea and vomiting may be a side-effect of anaesthetic agents or related to manipulation of the dura and meningeal vessels. With the anaesthetic regimens used at present, intraoperative nausea and vomiting occurs infrequently (<1%). Most reports describe administration of antiemetics as part of the local protocol for these procedures. Interestingly, the incidence of early postoperative nausea and vomiting is less after awake craniotomy than after craniotomy under general anaesthesia [66].

Problems with airway obstruction and respiratory depression during sedation can be minimized, but not eliminated, by careful titration of sedative and analgesics, patient positioning and close monitoring. Transiently decreased oxygen saturation, mild airway obstruction and decreased respiratory rate were noted in 18% of subjects during conscious sedation for craniotomy with awake brain mapping in a recent report [65] and at least one 30-s epoch of apnoea was recorded in 72% of patients undergoing asleep–awake–asleep craniotomy without airway instrumentation in another series [55]. Obesity has been described as a consistent risk factor for problems with inadequate oxygen saturation during intravenous general anaesthesia without airway intervention during asleep–awake–asleep craniotomy [64]. Although the jury is still out on the issue of airway management during asleep–awake–asleep craniotomy, there are now many reports describing placement of a laryngeal mask airway during the 'asleep' phase. The potential benefits of a laryngeal mask airway in this setting are that it provides a secure airway allowing for controlled ventilation if necessary and it permits titration of drugs during painful or stimulating parts of the procedure with less concern for respiratory depression. One group documented a lower incidence of airway complications with an asleep–awake–asleep technique with laryngeal mask airway placement compared with sedation without airway adjunct [67].

The potential for intraoperative hypoventilation or apnoea is one reason to have a back-up emergency airway management plan. Another is that emergent conversion to general anaesthesia is required in 1–8% of patients. Problems necessitating conversion to general anaesthesia include incomplete regional block that cannot be remedied, marked anxiety or agitation, postictal confusion and dysphoria. If conversion to general anaesthesia with controlled ventilation is suddenly necessary in a patient with an open craniotomy, under the surgical drapes, and in some cases with the head fixed in the pin head holder, ventilation and airway management may be challenging. Optimizing conditions for emergency airway management include positioning the patient initially in a manner that facilitates airway management (limiting neck rotation and flexion) and tenting the drapes in a manner that provides for easy access for airway management as well as neurophysiological testing. Laryngeal mask airway placement, even in the lateral position, has a high rate of success and is probably the rescue airway technique of choice in this circumstance [68]. Securing the airway with a laryngeal mask airway with the head in a pin head holder device is reported, although the success rate is not quantified [69].

Several series that have prospectively evaluated patient satisfaction suggest that most patients tolerate these procedures well, with 80–90% of patients reporting that they are either entirely satisfied or recall only minor difficulties [65,70,71]. Of note, when patients are asked what aspect of the procedure might be improved a repeated theme is postural discomfort. Padding, particularly under the flank and hip area and allowing limited supervised movement, reduces postural discomfort. Another comfort issue is the bladder catheter, particularly for male patients. If bladder catheterization will be performed (practice varies among centres) introducing lidocaine gel into the urethra at insertion decreases catheter-related discomfort in men and women [72].

Anaesthesia for epilepsy surgery in infants and children

When planning anaesthesia for epilepsy surgery in infants and children the anaesthesiologist has to keep in mind that some of the anaesthesia considerations for infants and children with intractable epilepsy who present for surgical therapy have been documented to be similar to adults, some are merely assumed to be similar and others are dissimilar or unique.

An illustration of how differences between children and adults might alter clinical anaesthesia management for epilepsy surgery is the higher incidence of topiramate-related metabolic acidosis in children than in adults [1]. This finding supports obtaining baseline blood chemistries in all children treated with topiramate who are about to undergo major neurosurgical procedures, a practice that will assist the differentiation of medication-related acidosis from acidosis due to more ominous diagnoses such as poor circulatory function or even malignant hyperthermia intraoperatively. An example of an anaesthesia management consideration documented to be similar in adults and children undergoing epilepsy surgery is that children, like adults treated with phenytoin and carbamazepine, are resistant to the non-depolarizing muscle relaxants rocuronium and vecuronium [73,74]. Nevertheless, in many circumstances the anaesthesiologist must be guided by inference from data obtained in adults. For example, oral

midazolam premedication is administered primarily to children. In adults taking phenytoin and carbamazepine both the plasma concentration and effect of oral midazolam are greatly reduced by induction of cytochrome enzymes [75] but data to confirm a similar effect in children are not available. Additional differences between children and adults that affect anaesthetic management for intracranial procedures for treatment of epilepsy are differences in the range of cerebral autoregulation, a greater likelihood of haemodynamically significant blood loss during craniotomy in children, a greater risk of intraoperative hypothermia in children, and differences in cognitive and emotional maturity.

Anaesthesiologists providing care for infants and children are more likely than those caring for adults to encounter patients on the ketogenic diet because the efficacy of this therapy is more clearly established in the paediatric population. Furthermore, the just-published results of a clinical trial that confirmed effective seizure reduction make it likely that anaesthesiologists will encounter more children on the diet in the future [76]. Although limited, some information is available to guide perioperative anaesthesia care [77–79]. A retrospective review of nine children (aged 1–6 years) on the diet, who received general anaesthesia (duration 20 min to 11.5 h) with carbohydrate restriction, found that although serum glucose levels remained stable there was a tendency to metabolic acidosis, particularly in longer procedures [78]. If the ketogenic diet is to be maintained perioperatively it is important to recognize that carbohydrates in liquid medications and chewable tablets and some blood products may be sufficient to reverse the ketogenic state. Also, as it is postulated that inadequate carbohydrate intake may be a predisposing factor for propofol infusion syndrome, the decision to maintain the diet may influence choice of anaesthetic for maintenance, and anaesthetic maintenance requirements might influence the decision to maintain the diet [80]. With attention to these metabolic and pharmacological nuances it appears that children on the ketogenic diet can safely undergo anaesthesia, even for prolonged procedures. Perioperative management should include measurement of electrolytes, serum albumin and calcium, which may be reduced, as well as repeated assessment of acid–base status and measurement of ketones and blood glucose levels. The ketone bodies beta-hydroxybutyric acid and acetone produce anaesthesia in animals [21]. Whether the ketosis in patients on the ketogenic diet affects requirements for anaesthesia has not been determined.

A number of syndromes are associated with intractable seizures in children. Syndrome-associated co-morbidities that may influence anaesthetic management include developmental delay and behaviour disturbance in children with Lennox–Gastaut syndrome, and developmental delay and angiomas of the central nervous system, mouth and airway in children with Sturge–Weber syndrome [81,82]. Children with tuberous sclerosis may have tuberous lesions in the heart (rhabdomyomas), kidneys and airway as well as the brain, with potential for a gamut of problems including renal dysfunction, lesion-related obstruction of blood flow, conduction disturbance, dysrhythmia and problems with airway management [83].

Awake intraoperative functional brain mapping and electrocorticography are not feasible in infants and many children. Thus, delineation of seizure foci by electrocorticography before cortical resection in infants and children is most often performed extraoperatively after craniotomy and placement of subdural grids or intraoperatively under general anaesthesia. Although the procedure is widely performed in this manner, the optimal anaesthetic for electrocorticography in children is not established. However, in a series of children with neocortical epilepsy the interictal spike frequency, although decreased by general anaesthesia with isoflurane (0.5–1%), reflected the awake interictal spiking pattern when intraoperative spike frequency was greater than one spike per minute [44]. At the author's institution, the protocol for general anaesthesia for electrocorticography during seizure surgery in infants and children is a combination of nitrous oxide, narcotic and inhalation anaesthesia. Pin sites and scalp around the planned incision are injected with local anaesthesia to minimize painful stimuli during light anaesthesia. Inhalation anaesthetics are discontinued and minimal end-tidal concentration is confirmed before commencing electrocorticography.

In older children and adolescents, awake intraoperative electrocorticography and awake intraoperative functional mapping are possible in carefully selected patients. Awake craniotomy has been reported in children as young as 9 years old [83]. Extensive preoperative counselling has been recommended. Adequate conditions for craniotomy with awake intraoperative brain mapping in children and adolescents undergoing epilepsy surgery with deep sedation and asleep–awake–asleep techniques with various anaesthetic agents including propofol and dexmedetomidine are reported [40,59,74,84].

The most common surgical procedures performed for the treatment of intractable seizures in the paediatric population are lobar and focal resections of the frontal and temporal lobes, followed by cerebral hemispherectomy and vagus nerve stimulator placement [85]. Cerebral hemispherectomy and placement of vagal nerve stimulator have some specific implications for anaesthesia management that warrant further elaboration.

Blood loss is the major issue for the anaesthetic management of cerebral hemispherectomy. The procedure is performed in infants and small children, who are at greater risk of haemodynamically significant blood loss during craniotomy than older children and adults. Frequent instances of marked precipitous blood loss, severe hypotension, coagulopathy, hypokalaemia and hypothermia have been described [86], as well as intraoperative demise due to uncontrollable bleeding. Although evolution of surgical technique has reduced the overall risk of these procedures, blood loss remains a major issue, with reported intraoperative blood loss greater than one blood volume in 25–50% of patients depending on hemispherectomy technique [87]. Safe conduct of anaesthesia requires excellent venous access and arterial pressure monitoring. At the author's institution central venous pressure monitoring, often via femoral venous catheters, is also frequently used, but practices vary. Blood products should be available in the operating theatre at the time of incision. In this and other intracranial procedures in children blood loss is difficult to gauge. The combined assessment of the several available haemodynamic parameters and serial blood sampling is required to guide fluid and blood product administration. Dilutional coagulopathy is predictable with blood loss in excess of one blood volume, and serial platelet counts, fibrinogen, partial thromboplastin time and prothrombin time are followed during the procedure to assess the need for component blood products, including

fresh-frozen plasma, cryoprecipitate and platelets. Even with blood loss that is less substantial, coagulation parameters should be checked intraoperatively to rule out a developing coagulopathy related to brain injury. Acid–base balance as well as P_aCO_2, P_aO_2, electrolytes and glucose should also be monitored at intervals during volume resuscitation. Loading doses of AEDs intended for postoperative seizure prophylaxis are given at the end of the surgical procedure so that drug levels are not reduced by ongoing haemorrhage. In our current practice the endotracheal tube is removed in the operating theatre in the majority of cases.

Vagal nerve stimulation is a new treatment modality for children and adults with seizures that are refractory to medical therapy. The vagal nerve stimulator device is placed during a surgical procedure that, in children, is performed under general anaesthesia. The device, about the size of a hockey puck, is positioned subcutaneously on the left chest in a manner similar to a cardiac pacemaker. The patient is positioned with the head turned to the right, a neck dissection is performed, and electrodes from the stimulator are wrapped around the mid-cervical left vagus nerve distal to branches to the atrioventicular node. Considerations, as outline above, for general anaesthesia in patients with chronic seizure disorders apply. If tested in the operating theatre under general anaesthesia, the absence of neuromuscular blockade allows for phrenic nerve stimulation to be detected on the capnograph waveform. Severe bradycardia leading to reversible asystole has been reported in 0.1% of device tests performed immediately after implementation [88]. Postoperative complications, which are uncommon, include unilateral vocal cord paralysis, which usually resolves over a period of weeks reported in 1% of cases, lower facial muscle paralysis, neck haematoma and airway compromise [89]. Chronic vagal nerve stimulation may cause a decline in respiratory function in patients with pulmonary disease and worsen symptoms of obstructive sleep apnoea [88].

Conclusion

Anaesthesia for epilepsy surgery describes a broad range of clinical situations and procedures. Each patient presents with a unique combination of neuropathology, medical conditions, concurrent pharmacological therapy and psychology. The best possible approach to anaesthetic management for many aspects of epilepsy surgery has not been defined. Clearly, a single recipe for success is not available. However, an understanding of the information available regarding the potential for anaesthetic agents to modulate seizure activity, the potential interactions between anaesthetic agents and drugs used in the treatment of epilepsy, and the particular requirements of the surgical procedure to be performed puts the anaesthesia team in the best position to contribute effectively to the multidisciplinary group working together to provide our patients with the maximum potential benefit of epilepsy surgery.

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81 Vagal Nerve Stimulation

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Introduction

Despite the availability of numerous antiepileptic drugs (AEDs), seizures in many patients with epilepsy remain refractory to medical therapy at maximum tolerated dosages. Vagal nerve stimulation (VNS) (VNS Therapy™ System; Cyberonics, Houston, TX, USA) is a non-pharmacological antiepileptic therapy that was approved in 1997 by the US Food and Drug Administration for use as adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial-onset seizures that are refractory to antiepileptic medications. VNS is also approved in numerous European Union countries for use in reducing the frequency of seizures in patients of any age whose epileptic disorder is dominated by partial seizures (with and without secondary generalization) or generalized seizures. As of June 2008, over 45 000 patients with epilepsy have been treated with VNS therapy (http://www.vnstherapy.com/Epilepsy/hcp/forsurgeons/implantedcomponents.aspx – accessed 6 June 2008).

Practical aspects

The VNS Therapy pulse generator, which is usually implanted in the patient's upper left chest, is powered by a lithium carbon monofluoride battery that produces charge-balanced waveforms at constant current. The latest single-pin version of the hermetically sealed titanium generator weighs 16 g and is 45 mm × 32 mm × 6.9 mm in dimension.

Before the operation is completed, diagnostic tests are performed to check the system for proper operation. At most centres, the generator's output current is then set to 0 mA for the first 2 postoperative weeks, after which ramping up of the output current is initiated. Other centres begin stimulation within the first postoperative day.

Clinicians set the parameters for automatic stimulation via computer software, which are then transmitted by the programming wand using radiofrequency signals to the generator (Table 81.1). Parameter settings for magnet-activated on-demand stimulation are also programmable. The wand is further used to perform diagnostic checks of wand–generator communications, lead impedance, programmed current and an estimation of the remaining generator battery life.

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The ramp-up procedure and settings for chronic, intermittent stimulation are individualized according to patient tolerance and clinical response. Besides intermittent stimulation, on-demand stimulation is achieved by the patient or a companion placing the supplied magnet on the patient's chest over the generator for several seconds. The stimulator settings used for on-demand stimulation usually utilize a higher current and pulse width than those used for intermittent stimulation. Some patients have reported that on-demand stimulation interrupts a seizure or reduces its severity and/or duration, particularly if applied during the early phase of the seizure [1]. Stimulation can be stopped temporarily by securing the supplied magnet over the device with tape or by inserting the magnet in an athletic bra over the generator. This may be necessary, for example, if the patient wants to avoid hoarseness while speaking, during eating if pre-existing dysphagia is present, during intense exercise if the patient experiences dyspnoea while exercising or at night if either stimulation-related discomfort or an exacerbation of sleep apnoea occurs.

The latest generator is estimated to provide 6 or more years of operation, assuming typical stimulation parameters, after which it can be replaced with a minor procedure performed under local anaesthesia.

Actions of vagal nerve stimulation and efficacy in animal models of epilepsy

Anatomy

The vagal nerve is a mixed nerve with regard to fibre size and direction of nerve transmission. Most vagal fibres are small-diameter unmyelinated C fibres; the rest are intermediate-diameter myelinated B fibres and large-diameter myelinated A fibres. Just as for other peripheral nerves, there are direct relationships between vagal fibre diameter and conduction velocity, and between fibre diameter and stimulation threshold. The threshold for C fibre activation is 10–100 times higher than for A fibre activation.

Special visceral vagal efferents innervate the pharynx and the larynx, the latter via the recurrent laryngeal branches of the vagal nerve. The general visceral efferents supply parasympathetic innervation to the heart (resulting in slowing of the heart rate), lungs (bronchial constriction and pulmonary secretions) and gastrointestinal tract (increased peristalsis and secretions).

Sensory vagal afferents constitute 80% of vagal fibres and transmit visceral sensation from the head, neck, thorax and abdomen. The cell bodies of the vagal nerve in the nodose ganglion project to the nucleus of the solitary tract (NTS). The NTS,

Table 81.1 Available stimulation parameter settings (Model 103 VNS Therapy).

Stimulation parameter	Available settings
Output current	0–3.5 mA in 0.25-mA steps ≤1 mA, ±10% > 1 mA
Signal frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%
Pulse width	130, 250, 500, 750, 1000 μs ± 10%
Signal on time	7, 14, 21, 30, 60 s ± 15% or ± 7 s
Signal off time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5–180 min (5–60 min in 5-min steps; 60–180 min in 30-min steps) +4.4/–8.4 s or ±1%, whichever is greater

in turn, projects to autonomic preganglionic and related somatic motor neurones in the medulla and spinal cord, and to the medullary reticular formation and the forebrain [2].

Most NTS output is relayed via the parabrachial nucleus (PBN), located in the dorsal pons lateral to the locus coeruleus, which sends efferents to the hypothalamus as well as the amygdala and orbitofrontal cortex [2]. The PBN has direct input to several thalamic nuclei, including the ventroposterior parvocellular nucleus, which relays visceral sensation to the insular cortex and the intralaminar nuclei of the thalamus, which have widespread effects on cortical activity. Both the PBN and the NTS project to the hypothalamus, amygdala and basal forebrain. The lateral hypothalamus and basal forebrain, in turn, project diffusely to the cerebral cortex and influence overall cortical activity [2].

Mechanism of action

The possible mechanism(s) of action of VNS are discussed elsewhere [2] and are clearly different from those known to be associated with pharmacotherapy, such as effects on neuronal membrane ionic conductance or neurotransmitters and their receptors. It is not clear, however, which of the observed effects are related to the anticonvulsant mechanism of action of VNS. Nevertheless, there are emerging clues. Krahl *et al*. [3] showed that chemical lesions of the locus coeruleus eliminated VNS-induced seizure suppression in rats, suggesting that the locus coeruleus is critically involved in the mechanism of action of VNS, possibly through the release of noradrenaline [3]. Furthermore, because increased γ-aminobutyric acid (GABA) transmission or decreased glutamate transmission in the rat mediocaudal NTS reduces susceptibility to limbic motor seizures [4], it is reasonable to hypothesize that VNS inhibits the rat NTS. The functional interrelationships between VNS, the locus coeruleus and NTS inhibition remain to be elucidated.

A study of transcranial magnetic stimulation in five patients treated with VNS for epilepsy showed significantly increased cortical inhibition associated with stimulation without any evidence of an effect on cortical excitability [5]. Further, in a limited series of patients whose seizures responded to VNS, Marrosu *et al*. [6] found normalization of impaired neuronal inhibition.

Animal studies

Vagal nerve stimulation has been investigated in a number of animal models of epilepsy. In most of these studies, stimulation was applied just before or immediately after the onset of a seizure [7–9]. Other studies evaluated the relationship between cumulative duration of vagal stimulation and seizure prophylaxis [10,11].

In male rats, VNS prevented or reduced clonic seizures that were induced by intraperitoneal pentylenetetrazole (PTZ) and 3-mercaptopropionic acid (an inhibitor of GABA synthesis and release), as well as tonic–clonic seizures caused by maximal electroshock [8], especially with stimulus frequencies and pulse widths of 10–20 Hz and 0.5–1 ms, respectively. In this model, the effectiveness of VNS directly correlated with the fraction of C fibres stimulated, consistent with another study in male rats that showed that penicillin-induced focal interictal spikes in male rats were reduced by 33% by direct C fibre stimulation [7]. Effectiveness also correlated inversely with the delay of stimulus from seizure onset – the greater the delay before vagal stimulation, the greater the seizure duration; therefore, stimulation worked best when applied as soon as possible after a seizure began.

In a dog model of strychnine-induced generalized seizures and PTZ-induced muscle tremors, VNS stopped seizures and tremors within 0.5–5 s when acutely applied [9]. Furthermore, VNS protected against seizures for a period that was four times longer than the duration of stimulation. Stimulation frequencies of over 60 Hz were less effective than slower frequencies, consistent with other studies [8].

In a study of both the acute and prophylactic effects of on-demand and intermittent vagal stimulation, VNS was administered at the onset of each spontaneous seizure or at least every 3 h for 40 s in an alumina-gel monkey model of spontaneous partial and secondarily generalized seizures [11]. Seizures were completely controlled in two out of four monkeys and decreased in frequency in the other two. Furthermore, the prophylactic anticonvulsant effect persisted into a stimulation-free period. No diminishment of interictal spike frequency was observed.

Takaya *et al*. [10] demonstrated that VNS protected against experimentally induced seizures even when discontinued before seizure onset. The anticonvulsant effect was nearly half-maximal 5 min after VNS was discontinued. In addition, they showed that 60 min of continuous VNS protected awake and freely moving rats from PTZ-induced seizures more effectively than 60 min of intermittent VNS with the same stimulation settings, and that intermittent stimulation was more effective than a single 1-min stimulus. Although it is impractical to apply continuous electrical stimulation to the vagal nerve due to safety considerations and limitations in battery life, these results suggest that the stimulation parameters used to treat seizures in humans are reasonable.

In cats, VNS applied during amygdaloid kindling significantly delayed the onset of seizures compared with control subjects and prevented the attainment of stage VI (generalized tonic–clonic convulsive seizures) [12]. The relevance of these results to patients with epilepsy is uncertain. Finally, a recent report in Genetic Absence Epilepsy Rats from Strasbourg showed no effect of VNS [13].

Epilepsy efficacy studies

The first pivotal trial of VNS was the E03 study, a multicentre, double-blind, randomized, parallel, active control trial of VNS in 114 patients with predominantly partial seizures [14–16]. The

second pivotal clinical study was the E05 study, a multicentre, double-blind, randomized, parallel, active control trial of VNS in 199 patients with complex partial seizures [17]. In 1991, a compassionate-use trial enrolled 124 patients with all types of intractable seizures (the E04 study) [18].

The E03 and E05 studies

Study designs

The E03 and E05 studies compared two different VNS stimulation protocols: high stimulation (30 Hz, 30 s on, 5 min off, 500-ms pulse width) and low stimulation (1 Hz, 30 s on, 90–180 min off, 130-ms pulse width). Low-stimulation treatment was expected to be less effective than high-stimulation treatment.

Study candidates were monitored over a 12- to 16-week prospective baseline period, during which seizures were counted and changes in AED dosages were allowed only to maintain appropriate concentrations or in response to drug toxicity. Patients who satisfied all inclusion and exclusion criteria were then implanted with the VNS system. Two weeks later, patients were randomized to receive either high or low stimulation. Over the following 2 weeks, patients randomized to the high-stimulation group had their generator output current increased as high as tolerated, whereas those randomized to the low group had the current increased until stimulation could be perceived. Efficacy was then assessed during the remaining 12 weeks of the treatment phase. At the conclusion of the study, patients were eligible to enter long-term open studies.

Enrolment information

Participants in the E03 and E05 studies were at least 12 years old, had at least six seizures per month during the baseline period, and were taking one to three AEDs. In the E05 study, patients had to have partial seizures with alteration of consciousness.

In the E03 study, 125 patients participated; 114 completed the prospective baseline and were implanted. The average duration of epilepsy was 23 years for patients in the high group ($n = 54$) and 20 years for the low group ($n = 60$). Patients in both groups were taking a mean of 2.1 AEDs at study entry.

There were 254 participants in the E05 study; 55 discontinued from baseline for failing protocol eligibility and 199 were implanted. One patient was not randomized due to device infection, and two randomized patients (one in each treatment group) were excluded from the analysis for administrative reasons. The baseline characteristics for patients in both groups were similar and consistent with the E03 study.

Results

In both studies, the primary efficacy analysis was percentage change in total seizure frequency during treatment relative to baseline, comparing the high- and low-stimulation groups. In the E03 study, the high-stimulation group had a mean reduction in seizure frequency of 24.5% versus 6.1% for the low-stimulation group ($P = 0.01$). In the E05 study, the mean percentage decreases in seizure frequency during treatment compared with baseline were 28% and 15% for the high- and low-stimulation groups, respectively. The between-group comparison was statistically significant in favour of high stimulation ($P = 0.039$).

Secondary efficacy measures in both studies showed statistically significant effects in favour of high stimulation. In the E03 study, 31% of patients in the high-stimulation group had at least 50% reduction in seizures compared with 13% of patients in the low-stimulation group ($P = 0.02$). In the E05 study, 11% of patients in the high-stimulation group had a reduction in seizure frequency greater than 75% versus 2% for patients in the low-stimulation group ($P = 0.01$). In addition, both the high- and the low-stimulation groups showed a statistically and clinically significant difference in within-group mean percentage change in seizure frequency during treatment compared with baseline ($P < 0.0001$).

Long-term efficacy

DeGiorgio *et al*. [19] prospectively evaluated seizure frequencies during a 12-month period in patients who had completed the E05 study, including patients who had been randomized to low stimulation during the E05 study but were then transitioned to high-stimulation settings as tolerated. The primary efficacy variable was the percentage change in total seizure frequency at 3 and 12 months compared with the 3-month preimplantation baseline. The median seizure reductions at 3 and 12 months were 34% and 45%, respectively ($P = 0.0001$, 12 months versus 3 months). In addition, one out of five patients had at least 75% or greater reduction in seizure frequency at 12 months. Retrospective analysis of changes in stimulation parameters showed that device changes were not the predominant predictor of increased efficacy after 12 months [20].

In a prospective study of 21 patients treated with VNS for a mean duration of 13.2 months, Tatum *et al*. [21] showed that reductions in numbers or dosages of AEDs without loss of seizure control and with improved patient satisfaction were possible in 15 (71%) [21]. In addition, seven patients were able to discontinue psychotropic drugs.

Other efficacy studies in epilepsy

Labar *et al*. [18] reported on 24 patients with medication-resistant generalized seizures and only generalized epileptiform activity or generalized EEG slowing. Epilepsy was idiopathic in seven patients and symptomatic in the remaining 17. Median seizure frequency was reduced by 46% after 3 months of stimulation compared with a 1-month baseline. Eleven patients had at least a 50% reduction in seizure frequency. The best responses to VNS occurred in patients with high baseline seizure rates and later ages of seizure onset.

Hosain *et al*. [22] studied 13 patients with Lennox–Gastaut syndrome (age range 4–44 years, mean 16.7 years) and found a median seizure rate reduction of 52% during the first 6 months of treatment (range 0–93%, $P = 0.04$) [22]. After 6 months of treatment, three patients had >90% reduction in seizures, two had >75% reduction and one had >50% reduction. No patient had a worsening of seizure frequency. Other anecdotal reports in patients with Lennox–Gastaut syndrome are similarly encouraging [23,24].

Among 12 children aged 4–16 years with medically and surgically refractory seizures who were treated with VNS, five patients had a greater than 90% reduction in seizure frequency and four patients were able to reduce the number of AEDs used

[25]. In another series of 16 children aged 4–19 years, six children experienced at least a 50% reduction in seizure frequency during the tenth to twelfth months of VNS [26].

Sixteen children with epileptic encephalopathy were treated with VNS and prospectively studied for changes in seizure frequency, EEG, adaptive behaviour, quality of life (QOL) and language performance [27]. One device was explanted due to infection. Of the remaining 15 children, four had at least 50% seizure reduction at 1 year after implant; conversely, two had at least a 50% increase in seizure frequency. Perceived treatment side-effects and general behaviour improved and in six children there was significant improvement in verbal performance that did not correlate with changes in seizure frequency.

Vagal nerve stimulation was studied in 60 children aged 3–18 years with pharmacoresistant epilepsy; 27% of these children had generalized tonic–clonic seizures [28]. After 6 months of VNS treatment ($n = 55$), the median reduction in seizure frequency was 31%. The corresponding figures at 12 and 18 months were 34% ($n = 51$) and 42% ($n = 46$), respectively. None of the adverse events required discontinuation of stimulation. Patwardhan *et al*. [29] reported reductions in atonic (80%), absence (65%), complex partial (48%) and generalized tonic–clonic (45%) seizures in an uncontrolled study of 38 children with a median follow-up period of 12 months (range 10–18 months) [29].

Six children under the age of 3 years with catastrophic epilepsy were treated with VNS and had a mean follow-up period of 42 months [30]. Four had a persistent improvement in seizure control, ranging from 60% to 90%.

Sirven *et al*. [31] studied the efficacy, safety and tolerability of VNS for refractory epilepsy in 45 adults who were 50 years of age and older [31]. After 3 months of treatment, 12 patients had a >50% decrease in seizure frequency; at 1 year, 21 out of 31 patients had >50% reduction. Side-effects were mild and transient, and QOL scores improved significantly during the first year of treatment.

Safety and tolerability of vagal nerve stimulation

The E03 and E05 studies

In the E03 study, safety and tolerability were evaluated with interviews, physical and neurological examinations, vital signs, electrocardiogram rhythm strips, Holter monitoring in a subset of 28 patients, gastric acid monitoring in 14 patients and AED concentrations. Similarly, safety and tolerability were evaluated in the E05 study with interviews, physical and neurological examinations, vital signs, Holter monitoring, pulmonary function tests, standard laboratory tests and urinalysis.

In the E03 study, the adverse events (side-effects) that occurred in at least 5% of patients in the high-stimulation group during treatment were hoarseness (37%), throat pain (11%), coughing (7%), dyspnoea (6%), paraesthesia (6%) and muscle pain (6%). Hoarseness was the only adverse event that was reported significantly more often with high stimulation than with low stimulation.

Table 81.2 Treatment-phase adverse events among patients treated with low or high stimulation in the E05 study [17].

Adverse event (*n*, %)	Low stimulation ($n = 103$)	High stimulation ($n = 95$)
Voice alteration	31 (30.1)	63 (66.3)
Cough	44 (42.7)	43 (45.3)
Pharyngitis	26 (25.2)	33 (34.7)
Pain	31 (30.1)	27 (28.4)
Dyspnoea	11 (10.7)	24 (25.3)
Headache	24 (23.3)	23 (24.2)
Dyspepsia	13 (12.6)	17 (17.9)
Vomiting	14 (13.6)	17 (17.9)
Paraesthesia	26 (25.2)	17 (17.9)
Nausea	21 (20.4)	14 (14.7)
Accidental injury	13 (12.6)	12 (12.6)
Fever	19 (18.4)	11 (11.6)
Infection	12 (11.7)	11 (11.6)

Only adverse events that occurred in more than 10% of high-stimulation patients are listed.

In the E05 study, none of the serious adverse events that occurred during the treatment phase was judged to be probably or definitely due to VNS. Implantation-related adverse events all resolved and included left vocal cord paralysis (two patients), lower facial muscle paresis (two patients), and pain and fluid accumulation over the generator requiring aspiration (one patient). The perioperative adverse events that were reported by 10% or more patients included pain (29%), coughing (14%), voice alteration (13%), chest pain (12%) and nausea (10%). Following randomization, the adverse events that were reported by patients in the high-stimulation group at some time during treatment and which were significantly increased compared with baseline were voice alteration/hoarseness, cough, throat pain, non-specific pain, dyspnoea, paraesthesia, dyspepsia, vomiting and infection (Table 81.2). The only two adverse events that occurred significantly more often in the high-stimulation group than the low-stimulation group were dyspnoea and voice alteration. Adverse events in both treatment groups were rated as mild or moderate 99% of the time. There were no sedative, visual, affective or coordination side-effects, or any cognitive changes. No significant changes in Holter monitoring or pulmonary function tests were noted.

Two E05 patients had VNS discontinued during the treatment. One patient in the high-stimulation group had two episodes of Cheyne–Stokes respirations postictally; after the device was deactivated, two more episodes were reported and the patient's mother requested that the device be reactivated. One patient in the low-stimulation group had the device deactivated due to a group of symptoms that the patient had experienced preimplantation as well as subsequent to device deactivation. No deaths occurred during either study.

As would be predicted from a non-pharmacological therapy, there were no changes in haematology values or common chemistry values in either study. Similarly, no changes in AED concentrations were seen.

Long-term safety and tolerability

Among a cohort of 444 patients who entered a long-term trial following participation in a short-term clinical study of VNS,

97% continued for at least 1 year, and 85% and 72% continued for at least 2 and 3 years, respectively [32]. The most commonly reported side-effects at the end of the first year of VNS were hoarseness (29%) and paraesthesia (12%); at the end of 2 years the most often reported side-effects were hoarseness (19%) and cough (6%), and at 3 years shortness of breath (3%) was the most frequently reported side-effect.

Hoppe *et al*. [33] studied cognition in 36 adult patients before and at least 6 months after implantation using tests of attention, motor functioning, short-term memory, learning and memory, and executive functions. No evidence of cognitive worsening was found.

The mortality rates and standardized mortality ratios of 1819 patients treated for 3176 person-years with VNS were contrasted with other epilepsy cohorts [34]. These rates and ratios were similar to those of other young adults with refractory seizures who were not treated with VNS. Additionally, the incidence of definite and probable sudden unexpected death in epilepsy (SUDEP) was 4.1 per 1000 person-years, which was consistent with other non-VNS epilepsy cohorts. Interestingly, the rate of SUDEP was 5.5 per 1000 over the first 2 years of VNS treatment, and 1.7 per 1000 thereafter.

Cardiac arrhythmias attributable to VNS in patients undergoing chronic stimulation have not been described, although Frei and Osorio [35] reported changes in heart rate and heart rate variability in a study of five subjects. In another study, high-strength stimulation produced no observable acute cardiorespiratory effects [36].

The possible relationship of VNS to swallowing difficulties was studied by barium swallow in a series of eight children [37]. Laryngeal penetration of barium was present in three patients without stimulation, and was caused by VNS in one other patient. Results from another small series of children treated with chronic VNS suggest that some children with severe neurological deficits who are dependent on assisted feeding may be at increased risk for aspiration if VNS occurs during feeding [38].

Anecdotal reports in the literature of complications of VNS have appeared as the number of patients treated with VNS has grown [2,39]. These reports include transient asystole lasting up to 20 s (approximately 0.1% of all implantations) during the intraoperative lead test [40–42]. The intraoperative lead test assesses stimulation function and system integrity by turning on the generator briefly at 1.0 mA, 500 μs and 20 Hz. Four patients had the device acutely explanted, whereas the others were chronically stimulated without difficulty. There were no sequelae in any of the patients.

As the VNS generator battery becomes expended, seizure frequency may increase in some patients [43] and others may note decreased or irregular perception of stimulation [44]. The end of battery service can be predicted with the current VNS model, allowing for elective generator replacement before the battery is fully depleted in those patients for whom VNS has been beneficial.

In a 2001 safety alert, the manufacturer cautioned against the use of short-wave diathermy, microwave diathermy or therapeutic ultrasound diathermy in patients implanted with the VNS Therapy system due to the possibility that the generator or lead could become hot and cause tissue damage or discomfort. At the time of the alert, there had been no reports of injuries related to these modalities in patients treated with VNS. Diagnostic ultrasound was not mentioned.

Clinical use of vagal nerve stimulation for epilepsy

Successful clinical implementation of VNS requires a team approach to implant the device, teach the patient and his/her family about its use, titrate the stimulation parameters to optimum clinical response, and monitor the patient's side-effects and the device's remaining battery life. Before implantation, patients should be counselled about the likely necessity of ongoing AED treatment, the possible delay in onset of efficacy and use of the supplied magnet to activate and turn off the generator.

Usual target stimulation parameters are shown in Table 81.3. Ramping up of the device typically occurs at outpatient follow-up visits every 1–2 weeks over the several months after implantation. At these visits, the current is usually increased by 0.25-mA increments to the maximum tolerated settings or until reduction in seizure frequency exceeds 50% compared with the pre-implantation baseline. If side-effects become intolerable or do not resolve following a change of stimulation parameters then the current is reduced by 0.25-mA increments as necessary. Reducing the pulse width may also improve tolerability [45].

If a patient's seizures have not satisfactorily improved with regard to frequency or severity after 6–9 months of stimulation, most clinicians would shorten the off time from 5 to 3 min. Subsequent staged reductions of the off time to 1.8 min and 0.2 min (with an associated decrease of on time to 7 s – 'rapid cycle') have been tried with success in some patients [46].

A minority of patients have the device explanted because of lack of sufficient efficacy. Based on the long-term efficacy studies it appears prudent to wait at least 12–18 months before deciding to remove the generator. Once the decision is made, the generator should first be turned off for several weeks or longer depending on the patient's preimplantation seizure frequency. If seizures then worsen for no other apparent reason it may be surmised that the device may have actually been efficacious for that particular patient and device removal should be reconsidered.

Explantation can be performed as an outpatient procedure under local anaesthesia. Because dissecting the helical coils off the vagal nerve is laborious and there are no reported complications of leaving them in place, most surgeons do not explore and

Table 81.3 Usual initial target stimulation parameters for VNS stimulation in patients with epilepsy.

Stimulation parameter	Setting
Output current	1.5 mA
Signal frequency	20–30 Hz
Pulse width	250–500 μs
Signal on time	30 s
Signal off time	5 min

remove the stimulating electrodes during the explantation procedure.

The application of VNS therapy will be enhanced once a measurable physiological response to VNS is identified that can be used to 'titrate' stimulation. In this regard, Koo *et al*. [47] used EEG findings at 6 months post implantation, including clustering and synchronization of epileptiform activity, to guide, with impressive results, further VNS programming in 20 patients [47].

Epileptologists generally consider VNS therapy as an option for patients (a) whose partial-onset seizures adversely affect QOL despite trials with three or more AEDs that are appropriate for partial seizures and that have been titrated to maximally tolerated doses and (b) who do not have surgically remediable partial seizures or who may, but are unwilling to undergo an intracranial procedure. The use of VNS in patients with generalized epilepsies at the present time is supported only by open, uncontrolled studies, although results are promising.

Conclusion

Vagal nerve stimulation is effective, safe and well tolerated in patients with long-standing, refractory partial-onset seizures [48], and may be beneficial to patients with other forms of epilepsy. There has been no indication of tolerance to therapeutic effect in long-term, open studies. Efficacy results for other seizure types and in children and the elderly are encouraging but are based on open studies or anecdotal experience.

Relatively few patients with medically resistant epilepsy become seizure free with VNS. There are suggestions that efficacy and QOL further improve over time [19,21,49–51], although published outcomes in long-term, open, unblinded studies should be interpreted cautiously. Given the possibility that efficacy may be delayed following implantation, it is prudent to wait at least 1 year, if not longer, before tentatively concluding that VNS has had no effect on seizure frequency or severity.

The most frequently encountered side-effects occur during the period of stimulation are usually mild to moderate in severity and resolve with reduction in current intensity or pulse width or spontaneously over time. Conspicuously absent with VNS stimulation therapy are the typical central nervous system side-effects of AEDs. Pending further studies, caution may be warranted when recommending VNS for patients with dysphagia, sleep apnoea and cardiac conduction disorders.

Further controlled studies should be performed to explore the use of VNS for generalized seizures and epilepsy syndromes. Additional controlled studies are also needed to determine (a) how VNS therapy can be individualized to maximize its effectiveness, either with intermittent stimulation or acutely with on-demand stimulation, perhaps triggered by automated seizure detection [52]; (b) whether VNS complements AEDs or non-AEDs with particular mechanisms of action; (c) how to prospectively identify patients who are most likely to benefit from VNS; and (d) the efficacy and tolerability of adjunctive VNS compared with adjunctive AED therapy, particularly early in the course of epilepsy.

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82 Brain Stimulation

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Introduction

Neurostimulation in the treatment of epilepsy involves stimulation of the brain or associated structures (e.g. vagus nerve). The goal of neurostimulation is to prevent seizures or reduce seizure frequency. Vagus nerve stimulation (VNS), currently the only Food and Drug Administration (FDA)-approved method of neurostimulation for the treatment of epilepsy, is the topic of the preceding chapter. VNS will not be discussed in detail here; the failure of VNS therapy to produce high rates of seizure freedom or responder rates much different than new antiepileptic drugs (AEDs) has stimulated the search for other methods and targets of neurostimulation for epilepsy treatment. VNS therapy has demonstrated that neurostimulation therapy avoids medication side-effects (e.g. cognitive) and is generally well tolerated. Although the actual mechanism of action of VNS and other neurostimulation therapy remains to be defined, it is generally thought that neurostimulation acts by different mechanisms from AED therapy.

Vagus nerve stimulation therapy provides extracranial stimulation of the tenth cranial nerve and its influences on epileptic seizures are via polysynaptic brainstem pathways with broad cerebral influences [1]. Although this offers the potential of cerebral neuromodulation, more recent efforts with neurostimulation have targeted intracranial structures in the hope that direct stimulation of intracranial regions, either with chronic or with intermittent stimulation paradigms, would be more effective than VNS. These intracranial targets for neurostimulation are discussed below.

There are several potential concerns about directly stimulating the human brain. As epileptic seizures represent increased excitatory activity, there are potential concerns that externally delivered excitatory stimuli may either be ineffective or possibly even cause seizures. Stimulation of subdural grid contacts in patients who are undergoing presurgical evaluations can, on occasion, trigger afterdischarges that may produce clinical manifestations [2]. The question as to whether direct stimulation of some human brain regions (e.g. hippocampus) could kindle the brain has been raised but not demonstrated. Unless the stimulating electrode is contacting a pain-sensitive structure (e.g. dura), chronic or responsive neurostimulation of intracranial structures produces no discomfort and indeed is typically not noticed by the patient. VNS therapy may produce some discomfort, although this typically is minimized with slow introduction of therapy over time [3].

Concept and requirements for programmed or chronic stimulation

The concept of neurostimulation in the treatment of epileptic seizures is based on two separate hypotheses that reflect the two basic types of stimulation. 'Chronic' or 'programmed' stimulation, somewhat like that used with the VNS but directed to other targets (e.g. hippocampus, thalamus), is hoped to provide modulation that will reduce the frequency of epileptic seizures. The mechanisms for the potential benefits of neurostimulation-induced neuromodulation are not established but one concept is that such stimulation may directly or indirectly reduce background synchrony. The normal brain has synchronous activity; indeed, all waveforms seen on the normal electroencephalogram (EEG) reflect synchronous cerebral activity – synchronous brain activity is not intrinsically undesirable. What is undesirable is the transition to abnormal synchronous activity that produces altered awareness and responsiveness (e.g. a complex partial or generalized seizure). Whether the transition to abnormal synchronous activity seen in a seizure is a gradual one or an abrupt state change is still unresolved, but desirable antiepileptic therapy, whether medical or neurostimulation, would reduce or prevent these transitions.

Reduced background synchrony could conceivably reduce or prevent the onset of partial seizures or affect the subsequent network recruitment and reduce or prevent secondarily generalized seizures. Although clinical trials of neurostimulation have been directed to treatment of partial seizures, conceivably thalamic or other deep brain stimulation (DBS) could benefit primary generalized seizures. Primary generalized seizures, however, are often readily controlled with medication, whereas only <50% of patients with remote symptomatic partial seizures have their seizures controlled with available therapies [4].

Chronic or programmed stimulation typically utilizes an open-loop system and as such the hardware requirements are much less sophisticated than with closed-loop systems (Table 82.1). The stimulating electrodes are placed in the target site (e.g. anterior thalamus) using stereotactic guidance and the electrodes are connected to the battery-operated stimulating device, which can be placed remote from the site of stimulation. Much of the experience with chronic stimulation devices is derived from the use of high-frequency DBS in movement disorders, both the treatment of tremor (essential and parkinsonian) and the motor fluctuations

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Table 82.1 Characteristics of neurostimulation for epilepsy treatment

Chronic stimulation	Responsive stimulation
External stimulator placement	External stimulator placement
Stimulating electrode may be at site remote from seizure focus	Stimulating electrode is targeted to be near seizure focus
Open-loop system	Closed-loop system
No event detection required	Designed to detect events with high sensitivity
Programmed periodic stimulation; chronic repetitive stimulation	Programmed to respond to detected events, intermittent stimulation
No option to review seizures	Can download and review detected events

and dyskinesias seen in drug-treated Parkinson's disease. Common targets for DBS in movement disorders include the thalamus, globus pallidus and subthalamic nucleus [5]. Risks of intracerebral haemorrhage with stereotactic placement of stimulating electrodes are in the range of 1–2%, and often these haemorrhages are small and resolve without deficits. The stimulation devices being used for chronic programmed trials of epilepsy treatment are similar to those approved for use in these movement disorders.

Concept of responsive neurostimulation

Epileptic seizures are brief, transient periods of focal, regional or generalized increased network synchrony and excitation. Partial seizures are rapidly evolving dynamic events, characterized by increased signal complexity, which include periods of seizure onset, organized rhythmic activity and intermittent bursting activity [6]. The onset characteristics of partial seizures from a given focus in a given patient are remarkably stereotyped as determined by both time–frequency decompositions and measures of signal complexity [6,7]. The typical partial seizure lasts less than 120 s [8] and spontaneously terminates with or without intervention. Patients in epilepsy monitoring units who have their medications reduced or withdrawn have more frequent seizures and more frequent secondarily generalized seizures but the seizures are still typically self-limited and not necessary longer [9]. Even patients with status epilepticus usually have recurrent seizures rather than continuous seizure activity, although the latter certainly occurs.

This concept of partial seizures as rapidly evolving, dynamic, but transient self-limited events has led to interest in interventions that could produce early termination of these events. The concept of responsive neurostimulation (RNS) is not to prevent the occurrence of seizures but to rapidly detect the seizure and deliver a stimulus that will alter the seizure dynamics and result in a brief seizure that is not disabling. RNS utilizes a closed-loop system that incorporates seizure detection hardware and software; detection then triggers therapy (Table 82.1). These closed-loop systems are considerably more sophisticated than simple open-loop systems.

As epileptic seizures are characterized by periods of increased synchronous excitatory network activity, the idea that external excitation may be beneficial is at first counterintuitive, but in fact there is experimental evidence supporting the potential therapeutic benefit. Studies in neural network models incorporating both excitatory and inhibitory neurones have shown that excitatory stimulation can terminate abnormal bursting activity [10–14]. Indeed, in these same model networks, termination can be produced when there is no functioning inhibition. This is not to say that inhibitory networks are not important in modulating human brain activity, just that inhibition may not be necessary for seizure termination, either spontaneous or triggered. The human brain and hippocampus comprise predominantly (80–90%) excitatory connections [15]. This has important implications for the application of responsive neurostimulation.

For responsive neurostimulation to be clinically beneficial, intervention has to be early, to prevent seizure evolution from an electrical or simple partial event (i.e. with no altered awareness) to a disabling seizure (complex partial or secondarily generalized). As partial seizures are being treated, it seems desirable to have the recording and stimulating electrode near the seizure focus to facilitate early detection and intervention before regional propagation, although more remote stimulation could still have potentially beneficial effects.

The fact that seizure onset patterns recorded from intercranial electrodes are very stereotyped facilitates early detection using computationally efficient detection algorithms that can be adjusted or tuned to the specific patient and their seizures so that seizure detection can be very sensitive. If a seizure could be predicted minutes before seizure onset then there is the potential for intervention even earlier with responsive stimulation [16]. At present, however, seizure prediction is at best very computationally demanding and cannot be carried out with small hardware devices, online, or with sufficient sensitivity to be reliably applied. This could change in the future, however, as the result of ongoing efforts to improve seizure prediction methods and applications.

Previous studies of chronic or programmed central neurostimulation

A number of cerebral structures have been targets for chronic or programmed brain stimulation. Cerebellar stimulation, the earliest target of therapy in humans, is discussed in the paragraph below in the historical context as this is no longer being investigated. More recently, the thalamus, hippocampus and subthalamic nuclei have been targets for modulation by high-frequency chronic neurostimulation. Although preliminary unblinded studies have been promising in a number of these areas, true measures of efficacy require evidence-based blinded trials. Because the brain is pain insensitive, the blind can be easily preserved (all patients are implanted and the placebo group is later stimulated) with central neurostimulation as the patient is not aware of whether stimulation is activated or not. As such, the blinding of central neurostimulation therapy is more easily undertaken than with VNS or medications. Typically in the neurostimulation trials, one investigator is unblinded to allow for adjustment of stimulation parameters. This investigator needs to be careful to 'preserve the blind' (e.g. to spend as much time with patients receiving therapy as those who are not).

Stimulation of the cerebellum

Stimulation of the cerebellum was one of the earliest attempts at treating epilepsy. One stimulation paradigm utilized two eight-contact strip electrodes, placed on the upper surface of the anterior lobe of the cerebellum through a burr hole or craniotomy and stimulus intensities of 1–9 mA, at 10 cycles per second, were used. In addition to implanting patients with epilepsy, cerebellar stimulation was used in attempts to reduce spasticity in patients with cerebral palsy [17].

The rationale for cerebellar stimulation as a treatment for epilepsy was not unreasonable. The cerebellum is known to modulate other brain activity and the cerebellar outflow tracts project to cerebral regions that modulate motor activity. The output from cerebellar Purkinje cells is inhibitory. Cerebellar stimulation had been shown to shorten trains of hippocampal discharges induced in humans [18] and to provide inhibition of cortical excitability [19].

Unblinded studies of heterogeneous patient populations [20–22] suggested that there were significant benefits in a majority of patients and hundreds of patients had cerebellar stimulators implanted – many for treatment of spasticity but not epilepsy. When a double-blind trial of chronic cerebellar stimulation in the treatment of epilepsy was performed, however, although 11 out of 12 patients subjectively reported improvement, there was no significant quantifiable reduction in seizures shown for any patient [23]. The safety of chronic implantation of intracranial strips was demonstrated with these studies. One might speculate that one potential reason for failure is that the resting firing rate of Purkinje cells is already quite high (e.g. 60–70 Hz) and that further stimulation might have relatively little impact on inhibitory cerebellar output. Whether larger blinded studies would have provided different results is not known, but cerebellar stimulation in humans for the treatment of epilepsy has been abandoned.

Chronic stimulation of the thalamus

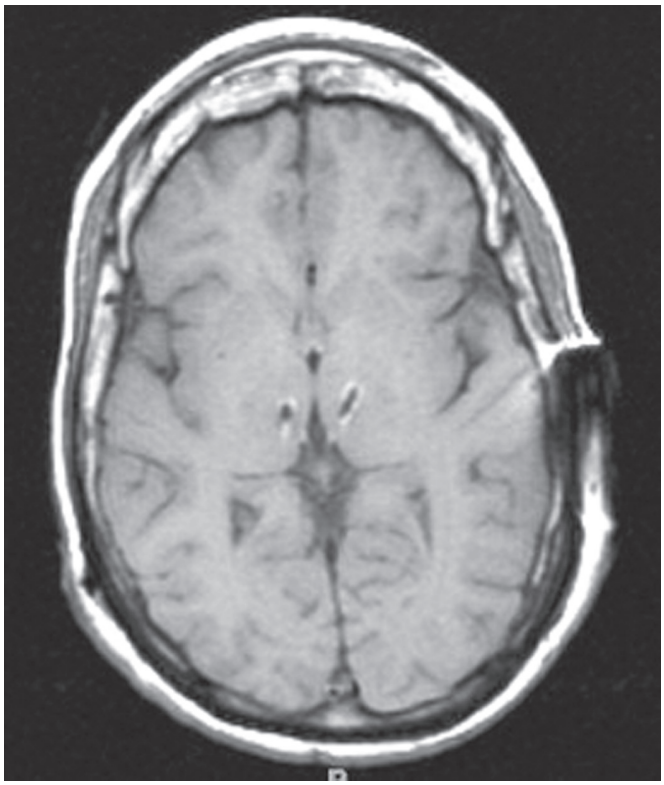
The extensive application of thalamic stimulation for the treatment of tremor and Parkinson's disease has provided considerable experience with long-term implantable devices for chronic, programmed stimulation. In the treatment of epilepsy, stimulation of both the central median nucleus of the thalamus and of the anterior thalamus has been tried. The thalamus is an important relay for afferents to the cortex and midline thalamic nuclei have strong connections with limbic regions [24,25]. Animal models have provided some evidence for medial thalamic involvement early in seizures [26]. A recent study [27] in kindled rats demonstrated that seizures were prolonged when drugs that either enhanced excitation (e.g. glutamate) or reduced inhibition (e.g. GABA antagonist bicuculline) were infused into the medial dorsal nucleus. These studies illustrated that pharmacological manipulation of midline thalamic regions could influence hippocampal seizure discharges, although typically the changes in duration were less than 50%.

Stimulation of both the centromedian (CM) and anterior (AN) thalamic nucleus is postulated to affect cortical synchrony [28]. Stimulation of the thalamus can influence the cortical EEG, and the EEG of the anterior thalamus is highly coherent with cortical EEG [29,30]. Electrical stimulation of the reticular nucleus in the rat suppresses kindled limbic seizures [31]. High-frequency stimulation of the anterior nucleus of the thalamus raises the clonic seizure threshold; however, low-frequency stimulation may be proconvulsant [32]. Anterior nuclear stimulation increased the threshold for motor cortex excitability in three patients [19]. A recent report of pilocarpine-induced seizures in rats suggests that stimulus intensity (500 μA better than 1000 μA) may be more important than stimulus frequency [33].

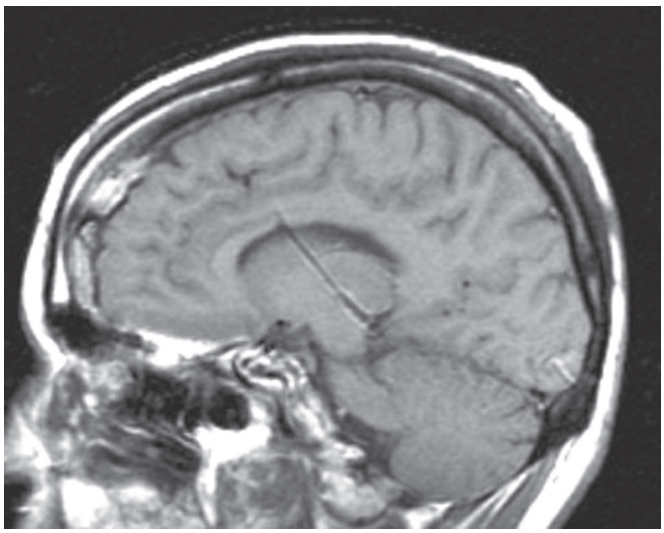
The first studies of thalamic stimulation targeted the centromedian thalamic nucleus (Fig. 82.1). Early unblinded studies of CM stimulation in patients with convulsive seizures suggested dramatic benefits [34]. However, a small ($n = 7$) randomized, double-blind, cross-over trial of CM stimulation in patients with medically intractable epilepsy documented a 30% reduction in generalized tonic–clonic seizures (GTCSs) with the stimulator on compared with an 8% reduction with the stimulator off (P = n.s.) [35]. In an open-label extension, no patient had a >50% reduction in seizures. Other uncontrolled small series have suggested benefit [36]. Additional later unblinded reports [37,38] suggest that GTCSs and atypical absence seizures have the best responses. In these studies of stimulation of the thalamic parvocellular centromedian subnucleus, best results are reported to be with bipolar stimulation at 60–130 Hz, 1 min on, 4 min off, with stimulation of alternating sides.

A recent review of chronic AN stimulation in the treatment of epilepsy has been published by Wennberg [28]. This review discusses many of the unanswered questions regarding AN stimulation and has a useful table summarizing the results of pilot studies to date. Early unblinded studies of chronic AN stimulation for the control of epilepsy have suggested benefit [39–43]. One pilot study [41] showed a significant reduction of seizure severity (e.g. secondarily GTCSs) with AN stimulation. Interestingly, as mentioned by Wennberg [28], the reported benefit for AN stimulation is not clearly associated with stimulation, as some patients who had been implanted and were not receiving stimulation also appeared to benefit [40,44]. Median stimulation frequencies have been typically 100–150 Hz (range 90–185 Hz). In the long-term follow-up of six patients with AN stimulation [44], five patients had ≥50% seizure reduction, although in two of these patients, as acknowledged by the authors, this level of benefit only occurred in years 5 and 6 when AEDs had also been changed. In the report of Lim *et al.* [42], AN implantation and stimulation produced a reduction in seizures of 49% in four patients, with one patient having ≥50% reduction in seizures; however, some patients in this study also experienced benefit during the sham period without stimulation. The best results from pilot studies were in the series of Osorio *et al.* [43], in which all four patients had ≥50% reduction in seizure frequency. This study, as noted by the authors, had a higher mean stimulus frequency (157 Hz) than other studies (~100 Hz). The maximum benefit was achieved at 10–12 months in these patients.

A multicentre controlled trial of AN stimulation, the SANTE trial (stimulation of the anterior nucleus of the thalamus for epilepsy), finished recruitment in 2007 [45]. This SANTE study enrolled patients with intractable partial seizures (with or without secondary generalization) and included an initial 3-month period when patients were randomized to stimulation or no stimulation, something that was not included in some of the pilot trials [41,43]. In contrast to chronic stimulation with VNS, DBS does not need to be ramped up slowly due to issues of patient comfort, as DBS



(a)



(b)

Fig. 82.1 Patient with bilateral stimulators in centromedian thalamic nuclei. T1 axial (a) and sagittal (b) MRI images are shown. The patient did not benefit significantly from the stimulation and the stimulator was turned off.

is painless. Still, studies of the efficacy of chronic stimulation need to be long term (i.e. >12 months) owing to potential neuromodulatory effects or if stimulus parameters are allowed to be adjusted to optimize effect. The most important measure of efficacy is obviously seizure frequency, particularly disabling seizures (complex partial and generalized tonic–clonic). Whether other measures of effect of chronic thalamic stimulation, such as measures of cortical synchrony, can be developed remains to be determined. Preliminary results just presented from the SANTE trial of anterior thalamic stimulation in humans have indicated efficacy with a median reduction in seizure frequency of 38% at 3 months and even greater efficacy in long-term studies (unpublished data presented at 2008 American Epilepsy Society meeting).

Chronic stimulation of the subthalamic region

Subthalamic nucleus (STN) stimulation has been demonstrated to benefit the motor symptoms of Parkinson's disease; many patients have received implantations for DBS [5]. Many of these patients are those who had become less responsive to dopaminergic agents or who had developed disabling dyskinesias and STN–DBS has provided considerable benefit. There is, therefore, as with anterior thalamic stimulation, considerable technical experience with targeting and implanting these structures.

Subthalamonigral inputs can influence amygdala-kindled seizures in rats [46] and suppression of nigral activity can be antiepileptic [47]. It is thought that the substantia nigra plays an important role in modulating seizures via forebrain mechanisms [48]. The STN provides excitatory input to the substantia nigra reticulata (SNr), and inhibition or suppression of this input could be antiepileptic by reducing the inhibitory influence of the SNr on midbrain regions that can be anticonvulsant [49]. The STN is a more discrete target for DBS than the SNr, is more easily approached, and there is considerable previous experience in the population with Parkinson's disease. Bilateral high-frequency stimulation of the STN (~130 Hz) suppresses seizures in a genetic rat model of absence [50]; other animal studies suggest that absence and clonic seizures benefit most. Not all seizure types may be suppressed with STN manipulation, with tonic seizures appearing resistant [51,52].

These experimental studies have prompted several small uncontrolled trials of STN–DBS in humans with refractory partial epilepsy. An early report of benefit (80% seizure reduction) in a single patient appeared in 2002 [53]. One preliminary report of three patients with refractory partial seizures found a mean reduction in seizures of 49% with all three patients benefiting [54]. Another report of STN high-frequency stimulation showed a 67–80% reduction in seizure frequency in three patients with medically refractory partial seizures, and one additional patient with severe myoclonic seizures (Dravet's syndrome) also responded, whereas a single patient with autosomal dominant frontal lobe epilepsy had no benefit [55]. Bilateral STN–DBS reduced partial seizures by about one-half and one-third, respectively, in two patients in another case report [56]. These preliminary studies most often utilize bilateral implantation and stimulation with frequencies of 130–185 Hz because animal studies have demonstrated that 130-Hz stimulation of the STN elevated seizure threshold, whereas stimulation at 260 Hz had no effect and 800 Hz stimulation actually lowered seizure threshold [57].

Additional blinded trials of STN stimulation in humans with intractable epilepsy are needed for evidence-based data supporting efficacy. Enthusiasm for pursuing these trials is muted somewhat by recently reported adverse effects of bilateral STN stimulation on working memory, and a growing number of reports of occasional undesirable behavioural effects [58,59].

Chronic stimulation of the hippocampus

In contrast with the anterior thalamus and STN, no anatomical or physiological justification is needed for the role of the hippocampus in complex partial seizures. The hippocampus is a common focus for complex partial epilepsy, and many patients with mesial temporal onset seizures have seizures that remain refractory to medical therapy. Patients with mesial temporal onset seizures, especially with associated mesial temporal sclerosis, are often excellent candidates for resective surgery. Resective surgery is a less desirable option in other patients with bilateral temporal lobe foci or seizure foci in functional regions of dominant temporal lobes. Although responsive stimulation can be directed to hippocampal regions (see below), other studies have used chronic stimulation paradigms.

Rat models (kainic acid) using limited programmed stimulation have demonstrated reduced interictal spiking during the period of high-frequency stimulation (200 Hz) [60]. In other studies by the same group, low-frequency stimulation (5 Hz) reduced the number of spontaneous seizures in the kainic acid model [61]. Low-frequency stimulation (1 Hz) of the amygdala can prevent kindling in the rat or suppress already kindled rats [62]. Studies in the low-calcium hippocampal slice model have shown that continuous intermittent stimulation (140 Hz) or continuous sinusoidal stimulation suppresses epileptiform activity [63]. Sinusoidal stimulation also suppressed bursting produced in hippocampal slices by high K^+ or picrotoxin. Interestingly, the suppression of epileptiform activity was greatest near the stimulation electrode. The group that has been most active in human studies has also reported that high-frequency stimulation (130 Hz) increases the threshold of afterdischarges in hippocampal kindled rats [64].

Two groups have reported small unblinded studies of the effects of hippocampal stimulation in patients with refractory mesial temporal lobe epilepsy. One group reported benefit from limited (2–3 weeks) stimulation at 130 Hz in patients who subsequently proceeded to temporal lobectomy. Stimulation reduced both seizures and interictal spike activity and did not appear to produce any pathological changes in this limited time [65]. Chronic stimulation of hippocampal structures has been reported [37]. The group in Ghent has the largest published experience with now 12 patients with refractory mesial temporal-onset partial seizures [66–69]. Although unblinded, the 12 patients were consecutive. Acute stimulation (7 days to 5 weeks) was performed (130 Hz, 450 μs) for 7 days with unilateral stimulation in the patient with unilateral seizures, including regional onsets ($n = 11$), or bilateral stimulation in one patient with bilateral independent foci. Two patients proceeded to selective amygdalohippocampectomy, one early in the study. Overall, 10 out of the 11 remaining patients had a >50% reduction in interictal spikes of sampled epochs. The one patient who did not have a reduction in interictal spikes proceeded to resective surgery and has done well. The other 10 patients entered a long-term stimulation period with a implanted pulse generator. Stimulation was typically 130 Hz but with one patient stimulated at 200 Hz. Mean follow-up was 31 (range 12–52) months and mean monthly seizure frequency during the last 6 months was compared with baseline. Two patients [with baseline complex partial seizures (CPS) frequencies of 4 and 6 months, respectively] were seizure free. Including these two patients, 8 out of 11 had ≥50% reduction in disabling (i.e. CPS or GTCS) seizures. Although AEDs could be altered after 12 months, this did not affect outcome. The only stimulus parameter altered was stimulus intensity; although this may affect a larger tissue volume, it is not clear that this provided added benefit. No increases in seizure frequency or afterdischarges were observed; stimulation was well tolerated. The investigators speculate that stimulation produces reversible increased local inhibition. They appropriately conclude that larger, randomized controlled trials are needed to determine efficacy.

A small blinded study of hippocampal stimulation by a group with considerable experience with anterior thalamic studies was reported recently [70]. The four patients selected were not ideal resective candidates because of potential risk to memory. Unilateral left-sided simulation was carried out through electrodes placed along the hippocampal axis, similar to the placement used by the Ghent group. One-month on periods were compared with 1-month off periods. Low-intensity stimulation was carried out at 190 Hz, 90 μs. During on periods, seizure frequency was reduced a median of 26% compared with baseline, and 15% compared with off periods. One patient who had highly refractory seizures and had failed contralateral surgery became seizure free after 4 months, regardless of whether the stimulator was activated. The stimulator was subsequently turned on to continuous chronic mode and she has been seizure free for 4 years. This group also appeals for larger randomized blinded trials of chronic hippocampal stimulation.

Clinical studies of responsive neurostimulation

The idea that electrical stimulation could terminate epileptic seizures (rather than cause them) was one that initially was questioned by some. As mentioned above, neural network models supported the concept that stimulation could result in early termination of bursting behaviour. Proof of principle trials in humans demonstrated that the afterdischarges produced on occasion during subdural grid mapping in humans undergoing presurgical evaluations for intractable epilepsy could be terminated by stimulation at low currents (<12 mA) [2,71].

With these preliminary results, human studies were first done using a NeuroPace external closed-loop responsive neurostimulation system (eRNS) [72]. These studies were carried out in patients who were undergoing invasive monitoring with subdural electrodes as part of their presurgical evaluations. The eRNS was connected in parallel, and detection parameters were adjusted to determine whether seizures could be reliably detected; this was demonstrated. If time permitted, without delaying surgery, the loop was closed and responsive stimulation was undertaken for a day or so. This study was not designed to demonstrate efficacy. Seizure detection could be carried out with high sensitivity. Responsive stimulations were well tolerated.

A safety and feasibility trial of the implantable NeuroPace responsive neurostimulator was next performed. This device is the only implantable responsive device undergoing controlled trials in humans at present [73]. The device (Fig. 82.2) is implanted in the skull (in a holder ferrule) and connected to intracranial leads (either depth arrays or subdural strips) that are placed near the presumed seizure focus. The implanted device contains a battery, programmable stimulator, digital processor and memory chip. The device, which is under the skin and muscle, can be

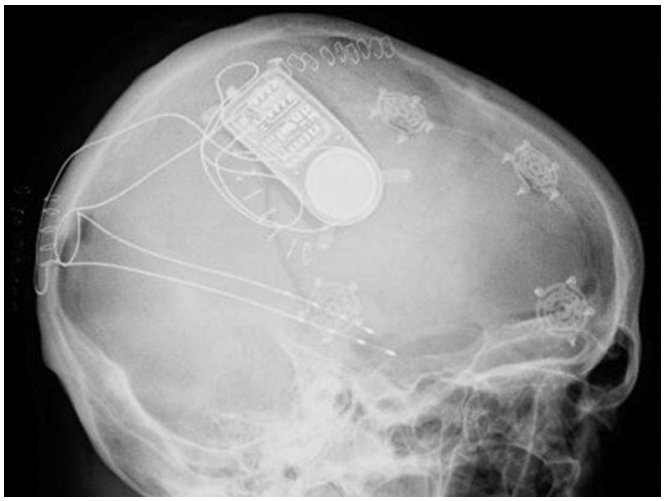


Fig. 82.2 Skull film of a patient with a NeuroPace responsive neurostimulator. The patient has intractable complex partial seizures with bilateral independent mesial temporal lobe foci (documented by previous invasive video-EEG monitoring). The two depth electrode arrays targeting the left and right hippocampal regions are seen connected to the NeuroPace responsive neurostimulator, which is inset into a ferrule recessed into the skull.

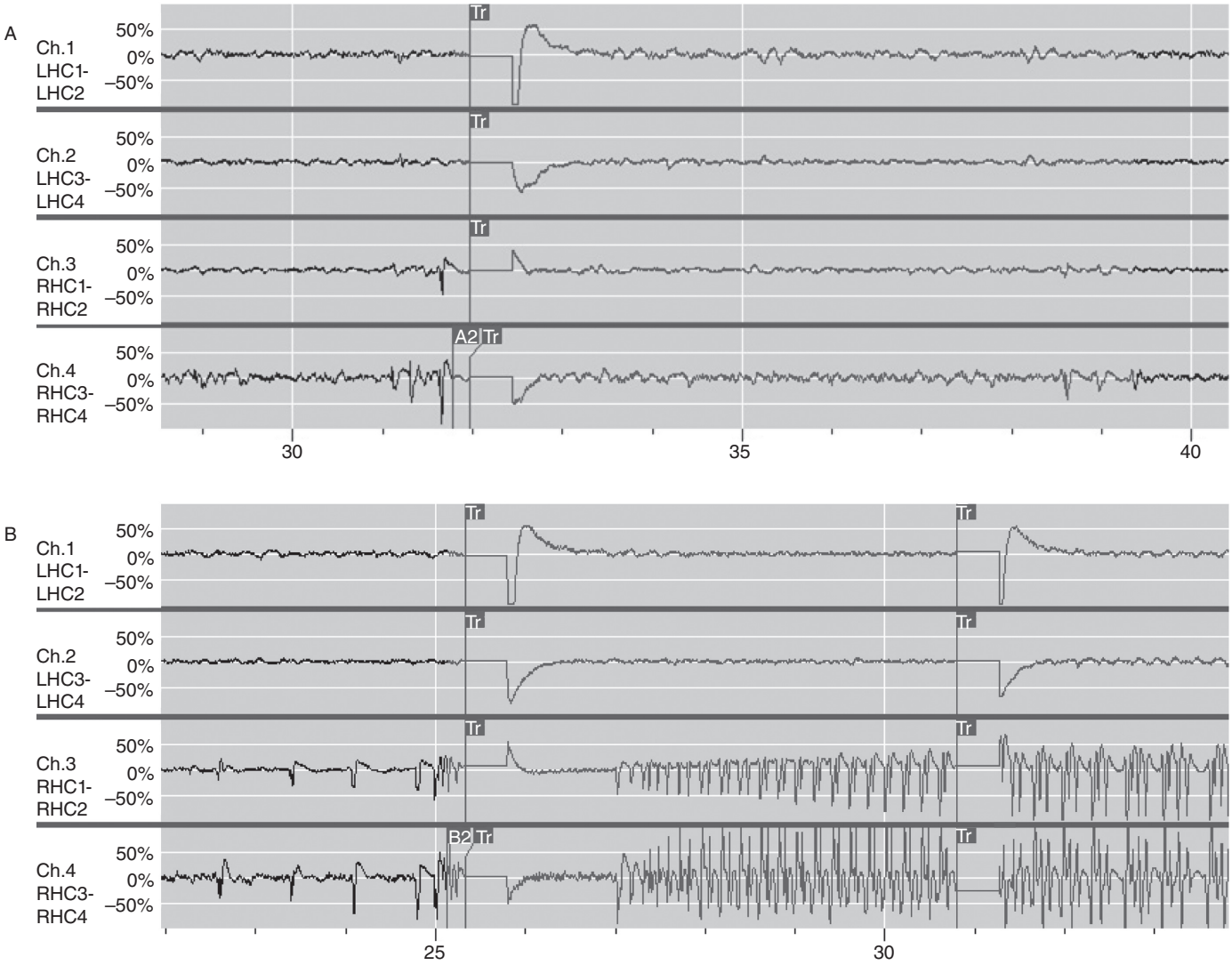


Fig. 82.3 Two epochs recorded from the patient illustrated in Fig. 82.2. These epochs were detected by the responsive neurostimulator and stored in the NeuroPace device and later downloaded by the patient. Channels 1 and 2 are bipolar recordings from the four contacts in the left hippocampus. Channels 3 and 4 are bipolar recordings from the four contacts in the right hippocampus. (a) A delivered therapy in response to detection of right-sided seizure activity. The detection algorithms were tuned to detect this activity within 2 s. No further evolution of seizure activity is seen after delivery of therapy; no clinical symptoms occurred. This may represent positive effects of therapy, although other interpretations are possible (see text). (b) Delivered therapy in response to another right hippocampal event. In this instance stimulation (two out of five are therapies are shown) did not prevent further evolution of seizure activity and a subsequent complex partial seizure.

painlessly programmed transcutaneously with a wand. In addition, the patient can download stored seizures and real-time EEG that can then be reviewed remotely. Storage capacity is limited by the size of the device, but all detections and stimulations are documented.

Seizure detection is tuned for the individual patient. Detection algorithms can incorporate one or more of half-wave, line length or area under the curve. When responsive therapy is activated, therapy is delivered after seizure detection (typically 2 s after seizure onset). Pulse frequency can range from 1 to 333 Hz, although typically frequencies of 100–200 Hz have been utilized. Single or multiple contacts can be stimulated. Each therapy can have two bursts and up to five therapies can be delivered for each seizure detection (Fig. 82.3). Total current is modest (up to 12 mA total for all stimulated contacts) with typical charge densities of <6 coulombs.

A safety and feasibility trial was conducted with this implanted device. This study was unblinded and was not designed to demonstrate efficacy. A total of 65 patients at 12 centres were enrolled and this study was completed in 2005. Some preliminary reports [73,74] have appeared. The device and repeated stimulation was well tolerated. Complex partial, generalized tonic–clonic and totally disabling seizures were significantly reduced by 40%, 55% and 41%, respectively [75,76]. As mentioned, this was not a trial of efficacy; in retrospect some non-responders had suboptimal placement of electrodes (e.g. remote from seizure focus) or multifocal epilepsy.

A pivotal, blinded trial of responsive neurostimulation is ongoing; recruitment was completed in late 2008. Thirty centres are participating with over 180 patients randomized. AED therapy is kept constant throughout the blinded portion of the trial (16 weeks), but detection and stimulation parameters can be adjusted.

The most important outcome parameter is number of disabling seizures (complex partial and secondarily generalized seizures). The original concept of responsive neurostimulation was not to prevent seizures *per se*, but to prevent seizure evolution after early detection. Assessment of the effects of RNS on a given event involves a number of factors. Figure 82.3 illustrates two right mesial temporal-onset seizures occurring at different times in the same patient. In the first instance (Fig. 82.3a), no further evolution of seizure activity after stimulation is seen. Although this may represent an effect of the delivered therapy, one cannot be certain that further evolution to a disabling seizure would have occurred without therapy. The second illustration (Fig. 82.3b) shows failure of the responsive therapy to prevent evolution of the seizure into a complex partial seizure. Failure or suboptimal responses to RNS therapy can result from a variety of potential factors, including the site of the stimulating electrode (i.e. proximity to seizure focus), the contacts being stimulated and the frequency of stimulation applied.

When the closed-loop responsive therapy system is tuned to be sensitive to epileptiform activity, it is triggered (with corresponding therapy) many more times than would be expected based on the seizure history of the patient. These stimulations are not triggered by false-positive detections *per se*, as they are triggered by epileptiform activity. Although it is possible to tune detection to be highly sensitive and specific for fully evolved seizures if, for instance, 20 s of activity was used, such specificity is difficult if one wants detection after 1–2 s. The net result is that patients with responsive therapy can receive a large number of delivered therapies. This appears to be well tolerated. If patients achieve benefit, however, it may be difficult to determine whether this is a result of the therapy directed at what would have been clinical events, or due to therapy directed to subclinical or interictal activity.

Conclusion

Neurostimulation for the treatment of epilepsy continues to hold considerable promise. Within the next year the detailed results of two randomized controlled trials will be available: the SANTE trial of chronic programmed stimulation of the anterior nucleus of the thalamus and the NeuroPace responsive neurostimulator trial. The pattern of previous unblinded trials of neurostimulation has been to overestimate efficacy. These blinded trials provide the best available data regarding responses to these two stimulation paradigms. The technology for neurostimulation is fairly well developed, although advances in battery life and storage capacity (for RNS) would be desirable. The potential benefits over AED therapy are appreciated, with no drug-related side-effects. It is hoped that the blinded trials will better provide evidence for responder rates than AED trials of new agents. Patients with certain seizure profiles (e.g. neocortical, mesial temporal) might achieve greater benefit.

Whether chronic programmed stimulation or responsive paradigms are more or equally effective remains to be determined. If responsive therapy is indeed better, then the future may see detection moved from early seizure onset to the preictal zone. One very real challenge is determining the optimal stimulation parameters for neurostimulation. These stimulation parameters may be different for chronic and responsive therapy, for different brain regions or even for different patients. Although this offers the opportunity for an infinite number of therapy options, in contrast to AED trials, it also presents one of the greater challenges to determining the most effective therapy.

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83 Stereotactic Radiosurgery for Medically Intractable Epilepsy

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Introduction

Radiosurgery is the precise application of focused radiation with stereotactic guidance to a targeted volume within the brain identified on magnetic resonance imaging (MRI) [1]. Conceptualized by Leksell for use in functional neurosurgery, radiosurgical treatment for neurological disorders has progressively widened its utility and is now also a treatment option for several neoplastic and cerebrovascular indications. In contrast to standard fractionated radiotherapy, radiosurgery delivers effective, precise and accurate radiation to a small volume without affecting large portions of normal brain parenchyma [2–4].

Approximately 20% of patients with epilepsy have seizures that fail to respond to medications. Despite modern advances in new antiepileptic medications, the percentage of patients with medically intractable epilepsy has not significantly improved. Patients with medically intractable seizures may be referred for surgical evaluation, and approximately one-half are found to be suitable candidates for resection of their seizure focus [5–8].

The most common type of open surgery performed for medically intractable epilepsy is an anterior temporal lobectomy, which is a resection of a portion of the temporal lobe [6,8–11]. With modern advances in surgical and anaesthetic techniques, microsurgical resection of mesial temporal lobe structures can be performed with relatively low morbidity. The inherent risks and possible complications of open surgery can be serious, however, and include hemiparesis, language and memory disturbances, and hemianopsia [12–15]. Several clinical studies evaluating the morbidity of open microsurgery for temporal lobectomy report that approximately 1–20% of medically intractable epilepsy patients who underwent open microsurgery had a symptomatic neurological postoperative deficit [9,12,13,16,17]. Furthermore, open procedures require several days of inpatient hospitalization including typically a course in intensive care. A significant proportion of patients with pharmacoresistant epilepsy, though, are deemed unsuitable for conventional microsurgery, as they may have an epileptic focus in difficult-to-access regions or in eloquent regions of the brain in which surgical resection could result in unacceptable and irreversible language, motor or visual impairment.

Radiosurgery is now being evaluated as an alternative treatment modality to open resective microsurgery for medically intractable epilepsy. High-dose radiation is toxic to all living cells, but the highly focused nature of radiosurgery allows stereotactic guidance and spares adjacent tissues from the damaging effects of radiation. At present, radiosurgery is under investigation as an alternative treatment modality for epilepsy associated with vascular malformations, gelastic epilepsy associated with hypothalamic hamartomas, and mesial temporal lobe epilepsy associated with mesial temporal sclerosis.

The two main types of radiosurgery are gamma knife and linear accelerator (LINAC). The original gamma knife was first developed in 1968 using a radioactive source of cobalt-60, which was placed in a helmet with central channels for irradiation using gamma rays. In the latest version of this device, hundreds of sources of radioactive cobalt direct gamma radiation to the centre of a helmet, in which the patient's head is inserted. The gamma knife uses multiple beams of radiation converging in three dimensions to focus precisely on a small volume, permitting intense doses of radiation to be delivered to that volume safely. A similar principle applies to LINAC, except that LINAC utilizes a different source of radiation produced by X-rays from the impact of accelerated electrons. Furthermore, for LINAC, the gantry must move in space to change the delivery angle of radiation.

Preclinical evidence

Preclinical studies investigating radiosurgery in animal models have demonstrated their potential utility when applied to models of epilepsy. Early animal experiments indicated the efficacy of focused radiation in a cat model of epilepsy to reduce seizure activity [7,18,19]. Using doses of between 10 and 20 Gy [one gray (Gy) is equivalent to one joule of energy per kilogram of tissue], cats with epileptic foci treated with a cobalt radiation source had reduced seizure activity. Histological tissue analysis of these treated animal specimens revealed 'neuronal reafferentation' as a proposed potential mechanism for seizure amelioration by focused radiation.

Sun and colleagues [20] report that focused LINAC radiosurgery successfully reduces seizure activity and raises seizure thresholds in a rat hippocampal kindling epilepsy model [20]. Seizure thresholds to external electrical stimulation were significantly increased and the length of afterdischarges was significantly decreased in the group treated with 40 Gy of radiosurgery. These antiepileptic effects were observed 1 week after radiosurgery treatment and persisted at the 3-month follow-up period.

In another model of chronic spontaneous limbic epilepsy in rodents [21], rats that received the lowest dose (10 Gy) of gamma knife radiosurgery showed no improvement in seizure activity, whereas the 20-Gy group exhibited a gradual and

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progressive reduction in seizure frequency between 2 and 6 months after radiosurgery treatment. Lastly, the 40-Gy treatment group displayed a dramatic reduction in seizures by the second month after radiosurgery. Histological tissue analysis of targets treated with radiosurgery in this animal study noted no necrosis in the tissue specimens. Instead, remnants of synaptically driven neuronal firing was found to be intact in these treated rodent brain slices, suggesting that neuronal death was not responsible for the identified seizure reduction.

A dose–response study for gamma knife radiosurgery was carried out in a kainic acid-induced epilepsy rat model [22]. Ten days after kainic acid injection, the epileptic focus was treated with a range of 20–100 Gy. The animals treated with the lowest dose of 20 Gy demonstrated a reduction in the number of daily seizures during each week of observation after radiosurgery. Furthermore, 3 weeks after radiosurgery, all treated animals at each radiosurgery dose – 20, 40, 60 and 100 Gy – showed a statistically significant reduction in seizure activity, confirmed by electroencephalography. Tissue histology revealed radiation-induced necrosis only at the 100-Gy radiosurgery dose. Another study using the same rat kainic acid–epilepsy model was undertaken to further evaluate the behavioural effects of these 'subnecrotic' radiosurgery doses [23]. Radiosurgery did not worsen deficits in a new memory attainment task with water maze testing compared with non-treated control animals injected with kainic acid alone (but both groups showed behavioural impairments when compared with control animals without kainic acid injection). Histopathological tissue evaluation of study animals confirmed that seizure activity reduction was not associated with tissue necrosis or a concomitant loss of neurons.

The long-term effects of radiosurgery were evaluated in rats that underwent a low radiation dose (35 Gy) of radiosurgery at 16 months after radiosurgery treatment [24]. At 6 months post irradiation, T2-weighted signal abnormalities suggestive of oedema were observed on MRI, and were most pronounced at 9 months. After 16 months, two out of six treated animals demonstrated radiation-induced necrotic cavities after treatment with a 35-Gy dose of radiosurgery. The four remaining treated animals without frankly necrotic cavities had other notable findings, such as severe atrophy of the corpus callosum, loss of thickness of the somatosensory cortex and damage to the striatum oriens hippocampi. These animal studies suggest that the full radiobiological and histological effect of radiosurgery may manifest only many months after radiosurgery treatment.

These preclinical studies report the amelioration of seizures as well as histological neuronal changes associated with radiosurgical treatment in different animal epilepsy models. Most of these studies suggest a dose-dependent effect of radiosurgery, with a minimum dose of about 20 Gy to see any therapeutic antiepileptic effect. Furthermore, the full histological effects may require several months to fully develop.

Clinical evidence

The first clinical application of radiosurgery for epilepsy was utilized by Talairach in the 1950s with the implantation of radioactive yttrium in patients with mesial temporal lobe epilepsy (MTLE) [25]. Further clinical experiences with gamma knife radiosurgery and linear accelerator (LINAC)-based radiosurgery for the treatment of arteriovenous malformations [4,26–32] and low-grade tumours have also reported incidental antiepileptic effects of radiosurgery treatment. Although it was not clear whether the effects on the epileptic lesion itself or the surrounding tissue accounted for the incidental seizure reduction, these clinical reports provided the original impetus for investigating radiosurgery as an alternative treatment for medically intractable epilepsy.

Mesial temporal lobe epilepsy

Mesial temporal lobe epilepsy associated with mesial temporal sclerosis (MTS) is perhaps the most well-defined epilepsy syndrome responsive to a structural intervention such as surgery. When temporal lobe epilepsy is due to underlying MTS, seizure improvements with open microsurgical structural resections has been reported to be between 65% and 90% of patients [6,8,33–37]. This form of medically intractable epilepsy is particularly amenable to radiosurgery because 80–90% of these cases show identifiable changes on magnetic resonance imaging (MRI), which is used to plan targeting and dose volume [2].

Recently, radiosurgery has been explored as an alternative treatment to open resective microsurgery for MTLE. In a small cohort of patients with MTLE, treated with gamma knife radiosurgery, Regis *et al*. [38] reported amelioration of seizures with minimal morbidity. A subsequent prospective, multicentre European study evaluating gamma knife radiosurgery for MTS-associated epilepsy showed similar efficacy rates (65%) for seizure reduction by conventional microsurgery or radiosurgery after 2 years of follow-up [39]. Using a marginal dose of 24 Gy, Regis *et al*. demonstrated that radiosurgery can be used as an alternative treatment to conventional resective microsurgery to effectively treat MTLE associated with MTS and improve quality of life with similar rates of morbidity and mortality. In the USA, a multicentre pilot trial is being conducted at present, with preliminary results showing that 85% of patients treated with 24 Gy (to the 50% isodose line) to the medial temporal lobe (including the amygdala, anterior hippocampus and nearby cortex) with 2 years of follow-up are seizure free with minimal morbidity (Barbaro *et al*., unpublished). This study group is also planning a larger, phase 3 multicentre trial comparing open microsurgery with radiosurgery for patients with clinically and radiographically defined MTS-associated MTLE.

Long-term results of gamma knife radiosurgery for MTLE were recently reported in two studies from France. In one paper, with a mean follow-up of 8 years, 60% of patients were found to be seizure free at last follow-up [40]. In the other French paper, with mean follow-up of 5 years, 47% of patients were reported to be seizure free [41]. In the five of 15 patients who had stereoencephalography findings showing that the epileptogenic zone extended beyond the mesiotemporal structures, the seizure control was less successful after radiosurgery. These studies show that radiosurgery provides improved long-term seizure-free outcomes in well-selected patients with mesial temporal lobe epilepsy. The actual efficacy and safety of this radiosurgery treatment procedure still awaits a larger prospective study. In all clinical studies con-

ducted to date the beneficial effects of radiosurgery have not been demonstrated immediately after radiosurgery. Typically, patients with MTLE treated with radiosurgery can achieve seizure reduction at 9–12 months and possible complete cessation of seizures between 18 and 24 months after radiosurgery treatment. A transient increase in partial seizures (auras) can be noted at approximately the same time when complex seizures decrease [39]. More than one-half of all treated patients may require corticosteroids to treat the radiation-induced delayed oedema associated with the initial radiosurgical effect, commonly 10–15 months post treatment [39]. The delayed effect of radiosurgery is an important consideration for radiosurgery compared with open surgery, as it may expose patients to the continued morbidity of ongoing seizures, including sudden unexpected death and traumatic injury. Two deaths occurred during the latency period in a case series of five patients treated with 'low-dose' radiation (20 Gy) [42].

In patients who failed radiosurgery, subsequent open resective surgery has provided an opportunity to evaluate the histopathological effects in human subjects. After a reduced radiation dose, Cmelak *et al.* [43] report no radiation-induced histopathological changes in tissues treated with 15 Gy of radiosurgery. In another series with two patients treated with 18 Gy, one patient was noted to have a necrotic focus with some prominent vascular changes consisting of vessel wall thickening, and fibrinoid and hyaline degeneration, whereas the other patient treated with this subtherapeutic dose showed no necrosis or vascular histopathological changes [44]. When treated with a higher, yet subtherapeutic, dose of 20 Gy, all five patients from a series reported from the Cleveland Clinic demonstrated histopathological necrosis, perivascular sclerosis, and macrophage infiltration upon resection and evaluation [42]. These reports suggest that significant reduction in seizures may only be observed with radiation doses of greater than 20 Gy. These radiobiological and histological alterations, such as necrosis and vascular changes, may be required for an effective anti-seizure effect to manifest. Thus, a dose that produces some tissue necrosis and histopathological effects without producing an excessive biological response such as oedema, for example 24 Gy, may be the optimal effective dose in the radiosurgical treatment of MTLE [4,38,45].

At present, the radiobiology of radiosurgery in the setting of MTS-associated MTLE is not yet completely understood. Although some preclinical studies have suggested an antiepileptic effect of radiation with subnecrotic doses [23], human clinical studies have suggested that a certain amount of tissue necrosis and histopathological changes may be required to see a significant amelioration of MTS-associated MTLE seizures. The importance of this issue on biological effect is that radiosurgical treatment of eloquent brain regions would be possible if an effective subnecrotic dose could be found.

In parallel with preclinical animal studies, clinical trials have suggested that a lower marginal dose of 20 Gy may be less effective in reducing seizures. Cmelak *et al.* [43] report unsuccessful seizure reduction with radiosurgery using a 15-Gy marginal dose. Kawai *et al.* [44] also report two cases of radiosurgery with unsuccessful antiepileptic effect with a marginal radiosurgery dose of 18 Gy. Finally, Srikijvilaikul *et al.* [42] from the Cleveland Clinic also report their series of ineffective radiosurgical treatment for seizure control with a 20-Gy marginal dose.

In summary, radiosurgery for MTS-associated MTLE is an attractive option because it is relatively non-invasive, with lower morbidity than major surgery. Conventional open temporal lobectomy surgery can also be pursued if the initial radiosurgical treatment is ineffective and after sufficient time has been permitted for the delayed radiosurgical antiepileptic effect after 3 years [39]. Its main disadvantage at present is the delayed response on seizure control during which time patients continue to suffer from the sequelae of seizures. The long-term effects of radiosurgery on cognitive and neuropsychological functioning are yet to be determined.

Hypothalamic hamartoma-associated gelastic epilepsy

Hypothalamic hamartomas are uncommon lesions with a prevalence of 1–2 in 100 000 and are commonly associated with precocious puberty, developmental cognitive delay and gelastic epilepsy. Typically, seizures associated with hypothalamic hamartomas are gelastic and medically refractory. These hypothalamic hamartomas are ectopic tissue consisting of glia, neurones and other neuronal fibre bundles.

Microsurgical resection of hypothalamic hamartomas has been reported to improve control of gelastic seizure activity but, owing to the technical and surgical difficulties of reaching these lesions in a deep and critical area, open microsurgical resection is often complicated, incomplete and associated with a high risk of neurological sequelae, such as motor, visual and hypothalamic deficits [46–49]. Recent small case series have reported varying rates of seizure remission (from 37% to 40%); however, all have noted significant improvements in behaviour, sleep quality and even learning [50–54].

A European prospective multicentre trial of radiosurgery treatment has enrolled 60 patients, 27 of whom have exceeded 3 years of follow-up [55]. Among these, 59.2% have an excellent result, with a dramatic behavioural and cognitive improvement, and are completely seizure free (37%) or have only rare non-disabling seizures (22.2%). No permanent neurological complications were observed, although three patients presented with a transient poikilothermia. This alternative treatment of radiosurgery for hypothalamic hamartoma-associated gelastic epilepsy holds great promise given the significant surgical morbidity associated with microsurgical dissection of hypothalamic hamartomas. In further investigations with larger series, longer follow-up must be conducted to establish the true safety and impact of this treatment option compared with open surgery.

Arteriovenous malformations

The potential efficacy of gamma knife radiosurgery in the treatment of symptomatic localization-related epilepsies is most evident in the treatment of arteriovenous malformations (AVMs). In a representative case series of 59 patients, Steiner *et al.* [56,57] reported seizure remission in 69% of patients with AVM and epilepsy. A recent large case series emphasized that the incidence of seizure remission is better with smaller AVMs [58]. However, Steiner *et al.* noted that seizures remitted independent

of radiological remission of the AVM, a finding that suggests that the effects of irradiation near the lesion, rather than the improvement of the AVM itself, may be important in control of seizures after radiosurgery.

Cavernous malformations

The most common presentation of patients with cavernous malformations is seizure. These congenital vascular malformations can cause haemorrhage and neurological insult but, more frequently, manifest as intractable seizures. Radiosurgical treatment for cavernous malformations is controversial because clear evidence for protection from haemorrhage and the risk of rehaemorrhage has yet to be established [59–61]. For example, the early Swedish experience determined that gamma knife surgery did not appreciably alter the natural course of cavernous malformation while exposing patients to radiation-induced complications that exceeded by seven times those expected for AVMs [62]. A recent retrospective comparison concluded that traditional open resection resulted in better seizure control and rebleeding avoidance than radiosurgery [63].

Although resective, open microsurgical treatment of cavernous malformations remains the standard treatment modality, a recent series by Regis *et al*. [59] suggests a role for radiosurgery in the treatment of seizures associated with challenging cavernous malformations near 'highly functional cortex' that may preclude open microsurgical resection [59]. Using a mean dose of 19 Gy in a series of 49 patients with refractory seizures, 59% of patients became seizure free at 2 years' follow-up after radiosurgery treatment [59].

Long-term radiosurgical complications

Although the long-term complications of radiosurgery are not yet fully characterized, it appears that these delayed risks are minimal. There are several reported cases of radiosurgery-associated 'radiation-induced' malignancies, but these reported cases are rare [64–67]. Much longer periods of follow-up must be investigated to fully characterize the possible long-term complications and risk of radiation-induced neoplasms, as the development of new radiosurgery-associated neoplasms may require decades to develop. A conservative estimate of this chronic delayed risk of neoplasm after radiosurgery suggests this rate to be 1% at 20 years post treatment. which may be a negligible risk of increased malignancy with radiosurgery. Nonetheless, this may be an important consideration in younger treated patients who have a longer opportunity for oncogenesis.

Antiepileptic mechanisms of radiosurgery

Although radiosurgery has been shown to reduce seizures in various forms of medically intractable epilepsies, the mechanism by which this abatement occurs is not well understood. It has been suggested that radiation itself has a direct antiepileptic effect that may operate through several mechanisms. As glial cells are more radiosensitive than neurones, Barcia-Salorio [68] proposed that low-dose radiosurgery may reduce glial scar formation, allowing increased dendritic sprouting and improved cortical reorganization, resulting in fewer seizures. Elomaa *et al*. have theorized that the antiepileptic effect of radiation is further mediated through effects of somatostatin [69]. Although the clinical results of the most recent human studies suggest that the therapeutic efficacy of radiosurgery is linked to histopathological changes and identifiable necrosis of mesial temporal structures, proof for this theory would need to come from direct observation and histological evaluation of tissue samples in patients in whom radiosurgery has effectively controlled seizures. This is unlikely to occur, as only patients with persistent seizures after radiosurgery are likely to undergo further open resective microsurgery.

Surrogate markers of radiation effect and radiobiology, such as imaging changes on MRI, have thus far shown variable results. Radiation-induced oedema typically becomes evident in most patients 9–15 months following radiosurgery (Fig. 83.1). However, these imaging findings are usually time limited and are often followed by focal atrophic changes. Thus, MRI changes may not be diagnostic or indicative of true radiation necrosis. Furthermore, our pilot clinical trials have shown that MRI changes and peak MRI effects were poorly correlated with post-treatment symptoms. The actual biomechanism by which high-dose radiation and radiosurgery reduces neuronal hyperexcitability to ameliorate seizures will probably not be found or elucidated from human studies.

Although preclinical evidence and the results from early clinical human trials suggest that control of seizures might be possible with doses of radiosurgery that were lower than those typically applied to tumours [70,71], recent case reports also demonstrate the failure of low-dose radiosurgery to control seizures [42–44]. Although failure of seizure control is easy to identify, it is a much more difficult task to determine that lack of seizure control is caused by an insufficient radiation dose. The time dependence of radiosurgical effects is also a confounding factor that has not been fully elucidated, and a consensus among different treating radiosurgical centres for when radiosurgical treatment has 'failed' has not yet been agreed upon. Furthermore, radiosurgery patients reported with inadequate seizure reduction commonly had radiation doses of 20 Gy or less, and these patients showed little evidence of radiation-induced necrosis or histopathological changes in their tissue specimens [42–44]. Thus, the best evidence to date from human and animal preclinical experiments suggests that there is a steep dose–response curve for seizure reduction and that some neuronal necrosis is required to produce seizure abatement. This suggests that the radiosurgery radiation dose required to reduce seizures is very close to the absolute tolerability threshold of human brain tissue.

Conclusion

Recent studies suggest that radiosurgery may be an effective and safe treatment modality for medically refractory epilepsy. Prospective trials with larger numbers of patients in multicentre studies will be required to establish radiosurgery as a standard alternative therapy to open surgery. Currently investigated indications are epilepsy associated with mesial temporal sclerosis, AVM,

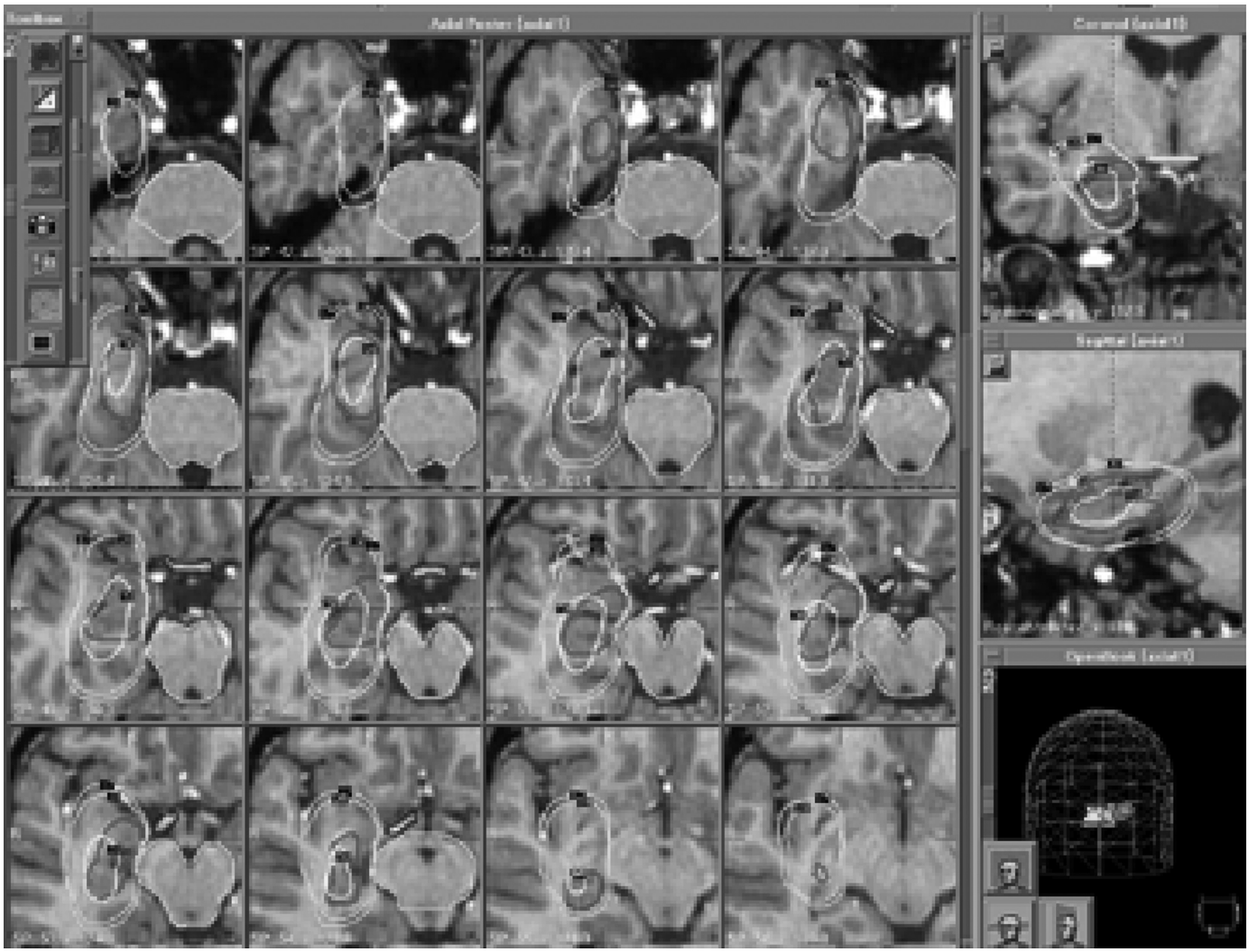

Fig. 83.1 Gamma knife treatment plan of the medial temporal lobe for MTLE with dosing curves.

cavernous malformation and hypothalamic hamartoma. Radiosurgery may prove to be especially appealing in treating lesions near functional cortex or deep-seated lesions when open microsurgical resection may not be feasible without significant morbidity.

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84 Future Focal Treatment Approaches to Epilepsy

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Introduction

As has been addressed in previous chapters, there have been considerable advances in antiepileptic drug therapy in recent years. In addition, both traditional surgical approaches and newer ablative/stereotactic methods, supported by neuroimaging developments, have also proved successful for many patients. However, despite these impressive achievements, up to one-third of patients continue to experience seizures on maximal tolerated therapy (see Chapter 2), for whom alternative strategies are urgently needed. Focal drug delivery and genetic and cell grafting techniques are newer strategies that are under development at present in this context. Focal cooling is also being explored (for a review see ref. 1) but will not be further discussed in this chapter. To date, almost all of the work is in preclinical experimental models, which cannot exactly model human epilepsy and which have limitations, but, nonetheless, provide a good basis from which future clinical studies might be developed. This chapter will consider the principles behind these focal treatment strategies, critically review the work to date and discuss if and when this might translate into new treatment options for currently intractable patients.

Focal treatment principles

Epilepsy represents the clinical endpoint of a wide range of aetiological processes but the common pathophysiological themes underlying seizures are well established, including hyperexcitability, altered inhibition and dysfunction of membrane channels. Many effective existing therapies target these known features by, for instance, increasing inhibitory transmission, interfering with excitatory transmission or modifying channel function. Almost inevitably when given systemically, such drugs have dose-limiting side-effects due to actions both outside the central nervous system and on non-epileptic brain regions. To this end, clearly a system that allowed delivery of drugs just to regions involved in seizure generation or propagation, rather than the whole brain, might be advantageous. Similarly, neuronal/stem cell grafts, or modification of genes in specific brain regions, might also prove beneficial with the potential to effect long-term local changes in the neurochemical environment, and to alter the structure and function of local neuronal networks. For any focal approach, there are a variety of sites in the brain that might be targeted (Fig. 84.1). The most obvious, as for surgical resections, would be the epileptogenic region, where this can be identified by imaging or electrophysiological means. Such focal treatment approaches, being less destructive and affording potentially more subtle manipulation than simple resection, might, for example, be applicable for many patients in whom resection or lesioning is not considered appropriate due to proximity to eloquent cortex. Second, when considering reflex epilepsies, for which the most common clinical scenario is photosensitive seizures, targeting the trigger site (e.g. occipital cortex) might be effective. Finally, for the many patients with multiple foci, or without a clear focal onset, manipulation of key propagation pathways might at least limit the clinical severity of seizures, if not completely prevent them. This is almost certainly the mechanism underlying vagal nerve stimulation (see Chapter 81) and other focal stimulation techniques (see Chapter 82) that are in clinical use and will not be further discussed here.

Focal drug delivery

The epileptic focus

The majority of studies have investigated the effects of GABAergic (γ-aminobutyric acid-secreting) drugs at the epileptic focus [area of maximal spiking on electroencephalogram (EEG)], as it is well established that GABAergic enhancement has an anticonvulsant effect. Thus, for example, in rats with seizures evoked by hippocampal bicuculline, a $GABA_A$ receptor antagonist [2], subsequent hippocampal infusions of diazepam (a $GABA_A$ receptor agonist) significantly reduced both clinical seizures and interictal EEG spiking. Several other compounds injected into the epileptic focus in a variety of models have also demonstrated antiepileptic effects, at least in the short term (Table 84.1). Although in some studies partial beneficial effects were also observed with control injections of vehicle substances, suggesting a non-specific effect perhaps related to the effect of cannula placement per se (e.g. unintended ablation or lesioning of the focus), the majority demonstrate convincing antiepileptic effects from a wide range of pharmacological modulations directed to the epileptic focus. However, these studies have largely been performed in acute seizure provocation models rather than more clinically appropriate models with spontaneous seizures, and mostly involve experimental paradigms which inevitably have a limited therapeutic

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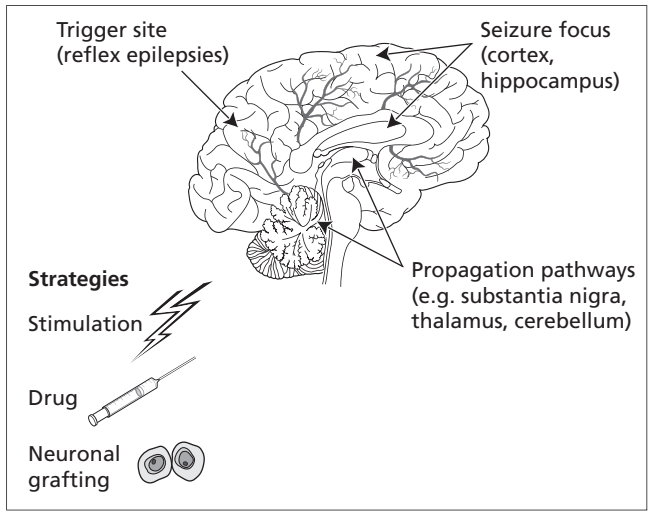

Fig. 84.1 Overview of focal treatment strategies.

Table 84.1 Positive focal injection studies into the seizure focus in rat experimental epilepsy models

Antiepileptic agent	Seizure model	Reference
Taurine	Amygdala electrical kindling	a
Lidocaine hydrochloride	Pyriform cortex bicuculline	a
Serotonin agonists	Hippocampal electrical kindling (cats)	a
Diazepam	Hippocampal bicuculline, cortical cobalt, systemic pilocarpine	a
mGluR II agonists	Amygdala electrical kindling	a
Glutamate antagonists	Prepyriform cortex electrical kindling	a
TRH	Amygdala electrical kindling	a
Adenosine	Hippocampal electrical kindling, cortical penicillin, hippocampal bicuculline	48, 49
Phenytoin	Cortical cobalt, cortical tetanus toxin	4
Gap junction blockers	Cortical tetanus toxin	50

All studies are in rat unless otherwise stated.
mGluR II, metabotropic glutamate receptor, group II; TRH, thyrotropin-releasing hormone.
[a] Reviewed in ref. 9.

time-course, lasting at most hours, so, at best, provide proof in principle. That said, when models with spontaneous seizures have been used, the results are still promising: in a well-characterized model of cortical epilepsy [3], refractory to several systemic agents, direct injection of phenytoin into the epileptic focus was effective without obvious behavioural effects, whereas high sedative doses of systemic phenytoin had no impact on the seizures, although the same did not apply to other tested AEDs [4]. This methodology also permits use of agents with widespread effects that preclude systemic use, such as gap junction blockers, which again show convincing effects at least in the short term [5].

Few studies have addressed the problem on a more long-term basis in spontaneous seizure models, although it is hoped that as technological developments that could facilitate such studies are rapidly advancing (e.g. osmotic mini-pumps, synthetic polymers and nanostructured materials), this will soon change. Remler and Marcussen [6] administered intravenous GABA to cats with a cobalt-induced focus and found little effect on the subsequent spontaneous seizures. However, if GABA was given, after local radiation to permeabilize the blood–brain barrier directly over the epileptic focus, then there was a significant suppression of spike activity, which was maximal 7–9 days after irradiation. Radiation itself had no effect on the seizures and the procedure was well tolerated with no obvious loss of function. The authors interpret the clinical effects seen as representing local delivery of GABA to the epileptic focus, although this was not directly confirmed. More recently, using the same model in rats, Tamargo *et al*. [7] used a surgically implantable synthetic polymer implanted over the epileptic focus. *In vitro* studies demonstrated continuous release of phenytoin (0.2–0.7% loaded dose per week) for up to 1 year, with loading doses that would theoretically deliver for up to 3 years in total. The *in vivo* efficacy studies included behavioural and electrocorticographic monitoring before and after implantation of phenytoin-loaded or sham polymers. In the treatment groups, both the incidence of clinical seizures (2 out of 9 animals versus 7 out of 10) and the mean electrocorticographic spike frequency (22/10 min versus 70/10 min) were significantly reduced compared with the shams, with no observed behavioural side-effects. Sadly, the seizures in this model spontaneously remit after 21 days or so, so *in vivo* data were only available for up to 2 weeks. Nonetheless, the results are promising and should be investigated in models with a more chronic epileptogenic region. Proof in principle of a focal drug delivery approach in man has also recently been published [8]: in patients undergoing resective surgery for refractory focal epilepsy, maximal spiking cortex was identified using intraoperative electrocorticography (EcoG). Subsequent direct application of lidocaine-soaked gel foam squares resulted in a clear reduction in spike count in all of the three patients studied.

The trigger site

Another potential treatment site for some patients with reflex epilepsies might be the brain area in which seizures are triggered. There are a number of established animal models of reflex epilepsies. The most widely used are genetically epilepsy-prone rats (GEPRs), in whom intense sound stimulation induces hyperlocomotion followed by clonic then tonic motor activity. These audiogenic seizures seem to be triggered from the inferior colliculus and can be suppressed for as long as 3 days with a group II glutamate metabotropic receptor agonist, and for shorter time periods with GABAergic agents or glutamate antagonists (reviewed in ref. 9). Longer-term drug delivery to a trigger site has also been achieved using an implanted mini-pump in the photosensitive baboon, *Papio papio* [10]. In this model, intermittent light stimulation induces bilateral myoclonus preceded by paroxysmal discharges, the neural generation of which has been localized in the motor cortex and has human parallels in some primary generalized epilepsy syndromes. These photoconvulsive responses were blocked during chronic 7-day infusion of GABA into the motor cortex (seizure focus), but also to the occipital cortex (trigger site), which was believed to carry the motor cortex afferents necessary for the induction of paroxysmal discharges. Perhaps surprisingly, there

were no observed behavioural effects in terms of either visual or motor function. In clinical practice, however, a trigger site is rarely identifiable other perhaps than in the context of photosensitivity, and even then it is hard to imagine an agent that might suppress photosensitivity without also affecting vision. Thus, although interesting experimentally, this approach is probably of less clinical relevance than targeting the epileptic focus/seizure onset zone.

Propagation pathways

In patients without an identifiable seizure onset or trigger focus, focal therapies may still offer the chance of at least disrupting the spread of seizure activity around the brain by targeting known key propagation pathways. The substantia nigra has been shown to play a critical role in the spread of seizure activity. In addition to electrical stimulation studies (see Chapters 81 and 82), various focally directed pharmacological manipulations in this region have proved to have at least partial effects in a range of acute seizure provocation and kindling models (reviewed in ref. 9). However, there are neither studies in spontaneous seizure models nor longer-term studies, and, as lesioning of the substantia nigra can produce similar effects and not all of the studies have adequate histological or pharmacodynamic data, whether observed effects represent specific pharmacological drug effects is not always clear. One big potential limitation in terms of clinical applicability is that GABAergic manipulations of the substantia nigra in rats seem to result in consistent side-effects, with unilateral applications producing turning and circling behaviour and bilateral applications inducing increased gnawing and sniffing. How this might translate to man is not yet clear but it is obviously of concern. In addition, as at best this approach seems to reduce seizure severity rather than reducing seizure frequency, it is dubious whether the benefits in all but a few individuals with severe frequent falls and convulsion would outweigh the risks involved.

Seizure-stimulated drug release

In most patients all but very localized minor seizures are associated with a detectable EEG change at onset, and in some this may precede the clinical event by a matter of seconds. Therefore, a further step on from chronic focal drug delivery might be to link seizure onset with acute focal drug delivery, which is an area under investigation. Using a computerized electroencephalography detection system in rats, Stein *et al.* [11] set up a linked, automated drug release system delivering diazepam into the seizure onset zone, which rapidly terminated seizure activity induced by hippocampal bicuculline in rats. In terms of automated electroencephalography detection this is a very preliminary study, and any such system in man would have to be very sophisticated to guarantee accuracy and protect against potential confounding factors, such as movement artefacts and triggering unnecessary release of drugs. However, patient-activated drug delivery systems might be devised for some patients who have a reliable clinical aura of sufficient duration.

Other focal drug delivery approaches

Other ways of targeting drug delivery to the central nervous system (CNS) are also under active investigation in a range of animal models, including epidural/transmeningeal delivery [12,13], which might carry less risk of damage to underlying brain, liposomal formulations of agents [14] and intranasal delivery [15] as a mechanism of at least partially overcoming difficulties related to blood–brain barrier penetration and CNS bioavailability.

As discussed, many of these studies have limitations but, nonetheless, they demonstrate a proof in principle that may open new therapeutic avenues for patients with identified but non-resectable epileptic foci, and potentially also for others with poorly localized onset by targeting known propagation or trigger pathways. However, even with the best of slow-release mechanisms or drug delivery systems, in the lifetime of an epilepsy patient, repeated implantation or refill procedures would be needed, with the attendant increasing risks of complications. In this context grafting of neuronal stem cells, particularly given the potential to manipulate their later differentiation, and for genetic modification in advance of implantation, might provide a more long-term solution. In addition, many epilepsies involve focal brain damage, which at least in principle might be repaired by neuronal grafts in the same way as has been applied in other conditions [16].

Genetic approaches to treatment

Molecular biology advances mean that now we can not only change the genetic make-up of cells *in vitro* before grafting into the brain (as will be reviewed in the next section), but also achieve modifications *in vivo* using recombinant viral vectors to insert genes into host cells in living brain. This is proving to be a very important research tool, enabling term expression of the inserted gene/relevant protein in a way that is not limited by either poor survival of grafted donor cells or the inevitable need to replenish drug delivery devices during the life of the individual. At present, adenoassociated virus (AAV) and lentiviral vectors look the most promising in the context of the brain, as they can transduce non-dividing cells, have an inherent preference for neurones and seem to result in long-lasting gene expression with minimal induction of host immune/inflammatory responses. AAV vectors, as recently reviewed [17,18], have been most widely used in epilepsy, as they can efficiently express therapeutic genes with a wide range of regulator elements, for example cell-specific/condition-dependent promoters, improving the efficiency with which alterations can be targeted to the key cell population that is believed to be relevant in the seizure model in question. This area is really still in its infancy, with most studies being focused on the induction of antiepileptic neuropeptides, such as galanin and neuropeptide Y (NPY), which look promising. Unfortunately, most studies to date involve transfection before the epilepsy/seizure-inducing insult in kindling or acute seizure provocation models, so are of largely mechanistic rather than clinical interest, although anticonvulsant effects are demonstrable. Two studies perhaps deserve specific mention, having shown what appears to be disease-modifying/antiepileptogenic effects in models with spontaneous recurrent seizures. The first of these [19] used AAV vectors to increase expression of $GABA_A$ receptor α1-subunit mRNA and protein in the dentate gyrus at 1–2 weeks after status epilepticus (SE), and

showed this to correlate with a threefold increase in mean seizure-free time after SE and a convincing 60% decrease in the number of rats developing epilepsy in the first 4 weeks after SE. The study is noteworthy in that it made novel use of a condition-dependent promoter, up-regulated after SE, to effect this change, although its clinical promise is hampered by the fact that AAV transfection was performed 2 weeks before the SE-inducing insult, and 30% of the transfected animals had excessive sedation, anorexia and weight loss persisting for the duration of the study. The more recent study used a more clinically relevant paradigm in which AAV transfection of the NPY gene was undertaken 3 months after electrically induced SE, in a well-characterized rat model with established spontaneous seizures [20]. In this model, the spontaneous seizures typically progress in severity and frequency over time, as was evident over a 2-week period of continuous video-EEG recording in sham-transfected and control animals. In a series of very carefully controlled experiments this progression was prevented by hippocampal NPY overexpression, despite the fact that immunohistochemical studies showed the biochemical effect to be limited to only 3 mm around the injection site. In addition to this antiepileptogenic effect, 40% of transfected animals had significant reductions in seizure frequency compared with their pretransfection baseline, thus supporting antiepileptic actions also athough all animals continued to have seizures. The Food and Drug Administration is said to be evaluating a clinical study based on this work [18]; whether this will prove practical at this stage remains to be seen, given that only a minority of patients with SE go on to develop epilepsy and that very anatomically accurate gene delivery appeared necessary.

Neuronal grafting

Repletion of depleted neurotransmitters

A number of studies have been conducted in experimental epilepsy and seizure models to address the potential for neuronal grafting as a treatment for epilepsy, and have been authoritatively reviewed elsewhere [17,21]. The majority of initial studies used similar experimental paradigms in which specific neurotransmitter inputs to the hippocampus (noradrenergic, cholinergic or serotonergic) are specifically targeted using physical or chemical means, increasing susceptibility to subsequent seizure provocations. This is followed by grafting, usually using cells of same-species fetal origin, with the aim of replenishing the previously depleted neurotransmitter and restoring seizure susceptibility to control (predepletion) levels. This type of study has been undertaken either in previously normal animals with subsequent electrical kindling or in models with established seizure tendencies such as the GEPR. The results of such studies (reviewed in ref. 9) are sometimes conflicting and are not always easy to interpret, given the variation in models, experimental detail and variable graft–host integration. Broadly speaking, however, particularly with respect to noradrenergic grafts, the results support that after specific neurotransmitter lesioning, appropriate fetal grafting can restore the targeted neurotransmitter levels to near normal, with some host integration and synaptic connectivity. In addition, as long as grafts are undertaken before any seizures have been provoked, then the seizure threshold is similarly returned to control (unlesioned) levels. These studies thus support the potential of neuronal grafts in terms of neurochemical restoration in epilepsy, but the real question is whether this approach can be utilized in models with spontaneous seizures in the absence of specific prior neurochemical lesioning.

Grafting fetal cells in other models

Sadly, when grafts similar to those described above have been undertaken in animals not subjected to prior specific neurotransmitter lesioning, or when grafting has been undertaken only after seizures have already occurred, results are mostly disappointing. Thus, even in noradrenergic depleted rats, the grafting of locus coeruleus noradrenergic cells after kindling seizures had been established produced no significant benefits [22]. Similarly, although GEPRs have been documented to naturally have both widespread deficits in noradrenergic function, and some serotonergic deficit before seizures occur [23], grafting of fetal locus coeruleus tissue into the lateral ventricles or inferior colliculus of GEPRs without additional prior noradrenergic depletion results in, at best, minor improvements that are unlikely to be of clinical significance [24]. Similarly, in the same model, others have reported no significant reduction in seizure severity with fetal locus coeruleus [25] or raphe [26] grafts to the hippocampus, although the power of such studies is often limited by small numbers and considerable variation in graft survival and integration.

Noradrenergic grafting has also been assessed in models without specific known deficits and in whom spontaneous seizures occur, which might be considered to be more appropriate to human epilepsy. The pilocarpine rat model has initial SE, following which the animals develop chronic spontaneous temporal lobe seizures with pathology similar to that of hippocampal sclerosis and additional widespread limbic forebrain damage. Bilaterally grafting cell suspensions of fetal locus coeruleus tissue into the hippocampus after SE in this model significantly reduced the number of spontaneous seizures in comparison with non-grafted animals and animals with grafts into the cerebellum or olfactory bulbs [27]. The decrease in seizure frequency, which occurred 6 weeks after grafting, when host integration would be expected to be maximal, was maintained for up to 15 weeks. However, it was not seen in all animals and, crucially, the study did not provide any histological evaluation of graft placement, survival, phenotype or integration. Thus, it is unclear whether the apparent treatment effect was in any way related to neuronal grafts as opposed to other non-specific focal effects (including hippocampal lesioning/destruction, which is of known efficacy) and further studies have not been reported. In contrast, implanting locus coeruleus cells bilaterally in to the hippocampus after pretreating with kainic acid, which produces a similar clinical phenotype, had no effect on subsequent kindling parameters [28]. However, the animals grafted with locus coeruleus cells did have fewer spontaneous seizures after kainic acid administration than control subjects, suggesting a mild treatment effect and illustrating that the outcome in provoked seizure models cannot necessarily be extrapolated to those with spontaneous seizures.

With the established efficacy of several licensed GABAergic drugs in epilepsy, and the promising results from initial focal drug

delivery studies, grafting of GABAergic neurones, which are most commonly derived from the fetal striatum, might be a more useful treatment strategy. Numerous studies have demonstrated that such grafts can survive, make axonal connections and restore GABA release in lesioned animals (reviewed in ref. 9), and there have now been a number of studies specifically addressing this in epilepsy. Fine *et al*. [29] increased seizure susceptibility by lesioning the caudate putamen with a glutamate receptor agonist, ibotenic acid, before grafting fetal striatal cells or a control graft of sciatic tissue into the substantia nigra pars reticulum. Unfortunately, both GABAergic and the sham/control sciatic nerve grafts reduced the severity of pilocarpine-induced seizures to almost that of the intact animal, and the survival of grafted neurones was not evaluated. Thus, this may represent a non-specific effect from lesioning the substantia nigra, although the treatment effects were slightly greater in the GABAergic grafted animals. Studies of fetal GABAergic grafts to the substantia nigra in fully kindled animals have been disappointing [30], producing only a transient initial increase in the threshold for eliciting focal epileptiform EEG activity, without any significant difference in clinical or electrographic seizure duration.

Hippocampal repair

Given the frequency of hippocampal sclerosis with its characteristic pattern of specific neuronal loss as a pathological substrate for human epilepsy, many investigators have concentrated on the therapeutic potential for neuronal grafts to effect hippocampal repair. Several animal models exist that mimic this pathology, usually with initial acutely provoked (electrical stimulation or chemical – e.g. kainic acid, pilocarpine) SE followed by chronic spontaneous seizures.

A series of eloquent studies in rats given unilateral intraventricular kainic acid are reviewed in ref. 21. This typically results in significant loss of CA3 pyramidal cells and glutamic acid decarboxylase (GAD)-positive interneurones, with relative preservation of CA1 and dentate granule cells. In this model, fetal hippocampal cells (either mixed hippocampal cell populations or those derived from the CA3 subfield) grafted into the lesioned hippocampus are associated with a restoration of total neuronal number, and, moreover, with limited damage to the host hippocampus by the graft itself. The grafts also appear to reverse or prevent other secondary pathological consequences. This includes aberrant sprouting of host mossy fibres into the dentate supragranular layer, thereby restoring the damaged cytoarchitecture, possibly by providing appropriate target neurones. The grafts themselves survive well, differentiate into mature neurones and form connections with host tissue; GAD-positive interneurone numbers are also restored, although it seems not directly from the grafted population. For good connectivity both the precise location of the graft within the hippocampus and the donor cell type appear to be important. All grafts (mixed hippocampus, CA1 or CA3 cells) showed good cell survival and sent projections to the ipsilateral septum, but only grafted tissue located in the degenerated CA3 cell layer and containing CA3 donor cells contained neurones that established robust projections to the contralateral hippocampus, resembling the projection pattern seen in intact animals. Similarly, grafts from the CA1 subfield had no effect on GAD-positive interneurone numbers, which the authors interpret as reflecting that the loss of CA3 afferents contributes to a secondary loss of the GAD protein expression, thus reversed only by repleting CA3 cells. The specificity and success of neuronal grafting to the hippocampus clinically could therefore depend upon matching specific cells to specific lesion types and, as the authors point out, in contrast to the kainic acid model, human hippocampal sclerosis involves damage to the CA1 region as well as the CA3 region and would therefore potentially require multiple grafts of appropriate cells.

A further problem is that grafting is most commonly undertaken only days after kainic acid lesioning in many of these studies, as it had been previously found that grafts implanted after this time resulted in steadily decreasing cell survival [31]. When cells were grafted 45 days post lesion, and examined 1 month later, cell survival had fallen to 31% [32] in comparison with 69% at 4 days post lesion [33]. It is not known when hippocampal cell loss in epileptic patients occurs but it is likely that any grafting would only be considered relatively late in the disease process and, inevitably, after seizure onset. However, survival 1 month after grafting appeared to be a good predictor of long-term (1-year) cell survival [34], and even the lower survival levels appeared to be sufficient to result in structural repair of the local damage.

The biggest limitation of these studies, however, is that the model did not exhibit spontaneous behavioural seizures (personal communication, A.K. Shetty, 2002), so no information on the potential therapeutic benefits of these grafts in terms of seizure outcome is available. It is also recognized that hippocampal cell death is neither necessary nor sufficient for epileptogenesis [35], so any repair that can be achieved may have little influence on the epilepsy although it may affect other clinically important parameters such as memory function. Other groups have found that grafts to both the intact hippocampus [36] or to lesioned hippocampi [37] may in some instances themselves be epileptogenic, with both electrographic spiking and occasional behavioural seizures occurring in previously non-epileptic animals. Thus, there are a number of concerns about the potential of attempted hippocampal repair as a strategy for neuronal grafting in epilepsy, particularly when balanced against the established efficacy of surgical resection of hippocampal foci in man.

Some studies have reported slightly more promising results. A study in a small number of amygdala-kindled rats showed that fetal hippocampal cells grafted near the CA2 region of the hippocampus reduced the severity of subsequent kindling-induced seizures to some extent in 80% of animals [38]. However, for most animals the seizure severity levels fluctuated with increasing number of stimulations, sometimes reaching pregraft levels. A very mild beneficial effect was also seen after transplanting hippocampal cells into the kainic acid-degenerated hippocampus. Although grafting had no effect on subsequent kindling-induced seizures, there was a slight reduction in the number of spontaneous seizures following the kainic acid administration [28]. More recently, Rao *et al*. [39] grafted hippocampal cells, with and without pretreatments (growth factors and caspase inhibitors) to improve graft survival, on to rats with spontaneous temporal lobe seizures following kainic acid-induced SE. The grafting was undertaken 4 months after the SE, when the animals had well-established seizures (a clinically relevant paradigm), and although there are no electroencephalographic data and small numbers

(five animals per treatment group), the results look convincing. In animals receiving untreated fetal hippocampal grafts, in which approximately 30% of grafted cells survived, no benefits were seen. However, in those receiving pretreated grafts, with 57–98% graft survival, seizure frequencies were up to 75% lower than those in ungrafted control subjects and also less severe. Interestingly, this seemed to correlate not with extent of hippocampal injury/restoration or hippocampal damage but simply with the presence of the graft per se, so the mechanism of this effect is unclear.

Overall with respect to hippocampal grafting/repair, work in this area is again still in its infancy. There is no conclusive evidence as yet that this approach will work; even if grafting in the first few weeks after an epileptogenic insult such as SE does prove consistently effective in animal models, clinical application will be difficult as the majority of patients with temporal lobe epilepsy do not have a clear initial insult and, conversely, many with the commonest insults (febrile seizures) do not ever develop epilepsy. Furthermore, many methodological questions (for example relating to cell type, strategies for enhancing graft survival, timing of grafting, etc.) need to be answered before we will know the real potential of fetal stem cell grafting as a treatment for epilepsy, and in our view it is unlikely this will translate into clinical practice within the next decade.

Transplantation of genetically engineered cells

Arguably, a more promising approach is to effectively combine what we know from focal drug studies and epilepsy therapeutics generally with advances in genetic and stem cell biology, by engineering cells for grafting that can effectively serve as a potentially permanent drug delivery reservoir. Several groups are now exploiting this potential, which, in our view, is the one most likely to directly benefit patients out of all of those that are discussed in this chapter.

GABAergic cell grafting

Initial studies using conditionally immortalized neuronal cell lines, genetically engineered to increase production and release of GABA by driving GAD_{65} expression [40], grafted to the substantia nigra in a limbic kindling model gave conflicting results depending on whether the graft was in the anterior substantia nigra (anticonvulsant) or posterior (pro-convulsant) substantia nigra, illustrating the complexity of seizure propagation pathways. The results of grafting this cell line in to the piriform cortex in the same model [41] were also disappointing, with only a very transient effect on seizure threshold before kindling, and no significant difference on any parameters after kindling. Grafting to the dentate gyrus [42] at face value looked a little more promising, with clear effects on subsequent afterdischarge threshold/duration and on kindled seizures. In the only published study by this group in a model with established spontaneous seizures [43], grafting to the substantia nigra in epileptic rats 2–3 months after pilocarpine-induced SE did reduce spontaneous seizures and epileptiform electroencephalographic activity more convincingly. However, a consistent problem faced by the investigators has been poor graft survival, <30% in the most recent studies even after a few days, which might in part explain the disappointing results, together with the possibility of down-regulation of GABA synthesis/receptors, and is certainly a barrier to moving forwards. Others have managed to achieve longer-lasting effects with immortalized GABAergic grafts to the substantia nigra, most recently including in a model of recurrent spontaneous seizures following kainic acid-induced SE in rats [44], although the benefits (30–50% reduction in the incidence of more severe, convulsive seizures) were perhaps modest, similar to those of new AEDs in the refractory epilepsy population.

Conversely, galactosidase (GAL)-labelled (encoded) human neural stem cells injected intravenously the day after pilocarpine-induced SE in rats [45] led to an impressive reduction in spontaneous seizures assessed 28–25 days later, with 87% of non-grafted animals developing spontaneous convulsive seizures compared with only 13% of the grafted group. Furthermore, subsequent *ex vivo* electrophysiological slice studies similarly demonstrated less excitability in the hippocampus of grafted animals. Histological studies showed GAL-positive cells throughout the brain, although few had mature neuronal phenotypes. In the hippocampus and piriform cortex, however, areas of maximal damage following pilocarpine SE, GAL-positive cells with GABA interneurone phenotypes were identified. The authors conclude that the neural stem cells have resulted in GABA-synthesizing cells in the injured hippocampus, thus suppressing spontaneous seizures; this is certainly plausible, although longer-term and more detailed experiments are required to take this work further and problems remain relating to identifying at-risk patients and the timing of grafting after any insult.

Adenosine

Adenosine is an endogenous neuromodulator with established antiepileptic and neuroprotective actions and, as such, is an attractive target in epilepsy. However, therapeutic use of adenosine or its agonists is largely precluded by significant peripheral and central side-effects, making it in many ways an ideal compound to explore using focal techniques. Initial work in this area used polymer-based drug delivery systems but has since moved on, as reviewed in ref. 46, to bring together technology from drug delivery systems, genetic engineering and stem cell grafting. Thus, studies involving paracrine release of adenosine from genetically engineered myoblasts and fibroblasts have each demonstrated clear antiepileptogenic potential, mostly studied in a kindling model. Long-term potential, as with GABAergic grafts, has been limited by poor cell survival. This group thus are now moving on to explore the use of technologies, such as encapsulation of grafts within synthetic polymers, or the use of biopolymer substrates to promote long-term adenosine release from encapsulated cells [47], which might provide some solutions and is certainly an area to watch. In addition, further studies in different models are needed, particularly when seizures are already established.

Conclusion

Epilepsy is a heterogeneous neurological condition and, despite recent advances, it seems likely that there will remain a significant cohort of intractable patients for whom other treatment approaches need to be developed.

At present many of the focal treatment studies have been carried out in experimental models with provoked seizures and there are still relatively few in good models with spontaneous chronic seizures, in part reflecting the practical difficulties and resource implications of long-term seizure monitoring in animals. If we are to develop strategies that might be translatable into clinical practice, which surely must be the primary aim, it is these long term studies that are now needed.

Focal drug delivery systems certainly show promise, although more detailed long-term studies in a range of experimental models, including behavioural outcomes, are needed. Neuronal grafting on face value holds the promise of effecting potentially permanent local change and initial studies demonstrate the feasibility of restoring neuronal loss, altering circuitry or increasing local neurochemical concentrations, all of which might prove beneficial in epilepsy. However, in addition to the limitations posed by the models used, the most promising results have arisen when the time between the initial insult and transplantation was short: (1) when specific known lesions and depletions were made before grafting and the appropriate type of grafted cells was used to match the lesion and (2) when therapeutic intervention occurred in advance of a chronic epileptic tendency being established. None of these scenarios can be applied to most clinical situations and it is recognized that grafts take less well to brain that is not acutely damaged, and that achieving long-term graft survival in cortical brain regions is especially difficult. Furthermore, although there is also increasing interest in antiepileptogenic treatments, which are often it seems perceived as a 'holy grail', it is a huge challenge to identify in practice which patients would benefit from such an intervention and at what stage in the development of their epilepsy.

Finally, whether considering focal drug delivery, genetic manipulation or grafting studies we do not yet know whether the benefits might only be transient, even with a permanent therapeutic local manipulation, given the known highly adaptable capacity of the brain in terms of receptor function and reorganization. The long-term ethical and safety aspects of using stem cell and genetic engineering approaches also require further careful scrutiny, particularly for epilepsy patients who have a normal life expectancy. Nonetheless, focal treatment techniques in epilepsy offer a novel approach to an important clinical problem and the promise that more patients may lead seizure-free lives with ongoing work in this field in the years to come.

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85 Epilepsy Surgery in Countries with Limited Resources

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Introduction

Ten years ago, the International League Against Epilepsy (ILAE) included in one of the main sessions of the International Epilepsy Congress in Prague a talk on epilepsy surgery in developing countries [1]. The preparation of that talk led to a reflection on the issue and to a review of the pertinent literature available at the time. Furthermore, it prompted a debate on the issue with experienced epileptologists from some of the main epilepsy centres in develop*ed* countries and also stimulated consultations on the issue with a number of specialists from develop*ing* countries who were involved in selecting patients with refractory seizures for surgical treatment, with the constraints imposed by limited resources. A couple of publications resulted from that initiative [2,3].

Here, it is interesting to note that some predictions made 10 years ago have become reality, particularly that technological and conceptual advances promoted by epilepsy centres in developed countries have indeed helped to streamline presurgical evaluation and surgical decisions in epilepsy programmes of countries with more limited resources. Below, it will be demonstrated that research conducted by technologically sophisticated centres has translated into simpler and effective strategies to evaluate patients for surgery in poorer regions of the globe. Such efforts in the industrialized world to support and disseminate advances that make epilepsy surgery more cost-effective are already aiding thousands of people in developing countries who need not suffer the consequences of medically refractory seizures [4,5]. In countries of limited resources, where the implementation of epilepsy surgery centres has proved successful, epileptologists and neurosurgeons have found financial and academic support to train in well-established epilepsy centres from richer countries. Such training has been crucial to promote the effective 'blending' of the knowledge resulted from high-class clinical research with the development of realistic protocols to be in applied in emergent epilepsy centres in developing countries.

This chapter reviews the evolution of epilepsy surgery in countries with limited resources. It starts by emphasizing the need for epilepsy surgery in these countries and then explores how clinical research conducted in technologically developed countries is impacting on the approach to refractory epilepsy in countries with limited resources. A discussion follows on how epilepsy centres in these latter countries are organized in order to offer surgery as a treatment option in epilepsy.

Before starting, attention to some important issues must be drawn. Firstly, it should be understood that there are two levels of heterogeneity in this discussion. At one level is the fact that expertise and technology in some countries of limited resources are similar to those in the developed world, whereas in others the gap is profound [6,7]. At another level, inequalities of access to good-quality of care *within a given country* are also a source of heterogeneity. Because the latter is a crucial issue, the views expressed here will be biased to what is offered by public health systems in countries with limited resources. A second point is that it is important to avoid a naive view of epilepsy surgery and accept that different centres approach a given 'epilepsy scenario' in different ways. Thus, some of the statements to be made here will not meet with unanimous acceptance – to say the very least. Nevertheless, in a field lacking randomized, controlled trials comparing the efficacy and/or the effectiveness of different evaluative or resective procedures, this is an unavoidable debate. Finally, it is commonplace in epilepsy surgery texts to stress diagnostic and localizing aspects of refractory epilepsies, putting less emphasis on the role of the surgeon's knowledge about epilepsy and his/her technical abilities to resect epileptogenic tissue. Clearly, there is no point in launching an epilepsy surgery programme without a good epilepsy surgeon. Developing countries are home to some extremely capable neurosurgeons, and the importance of getting them interested in joining an epilepsy team cannot be overemphasized.

The need for epilepsy surgery in countries with limited resources

The establishment of specialized epilepsy centres in developing countries makes sense epidemiologically, and has been instrumental in providing good-quality training programmes. Epileptologists who are trained in these centres can then provide much better care for patients with epilepsy in the community and also become regional leaders in the field. In addition, the establishment of such centres has allowed access to surgical treatment for a significant number of patients with surgically remediable epilepsy syndromes.

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Approximately 90% of persons with epilepsy live in developing countries [6–10]. Thus, 90% of epileptic patients who could potentially benefit from surgical treatment live in these regions, providing an important ethical argument for the establishment of epilepsy surgery programmes in developing countries. A treatment modality exists which can significantly alleviate disability for large numbers of people with refractory epileptic seizures; therefore, there is an ethical obligation for those involved in the care of these patients to pursue all possible avenues in order to make this treatment modality available where it is most needed.

Moreover, developing countries appear to have a greater prevalence of epilepsy, with figures ranging from 15 to 20 per 1000 persons [8,9,11], as compared with develop*ed* countries, where the prevalence is closer to 4 to 10 per 1000 persons [12,13]. Suboptimal obstetric care, poor regulation of driving and working conditions, and the general health (including poor nutrition) are partially responsible for this difference.

An ongoing challenge is to reconcile the need for expertise with the need to make epilepsy surgery widely available. The most important resource to implement successful surgical programmes is well-trained personnel. As will be further discussed below, advances in epileptological research have streamlined the processes of presurgical work-up for a large proportion of surgically remediable epilepsy syndromes. However, the only reliable way to translate these advances into practical and effective protocols for countries with limited resources is through solid training of the specialists who will lead the process. As alluded to in the introduction, the best models involved the interaction between specialists who have been trained abroad and their local colleagues, boosting development of regional epilepsy surgery programmes. More recently, there has been a move towards new specialists being trained locally, at least in some centres in countries with limited resources, such as Brazil.

In countries with limited resources, it is counterproductive to confuse the minimum with the ideal requirements for an epilepsy surgery programme and, thereby, postpone the benefit for those who can be helped immediately [1–3]. Epilepsy centres in developing countries should not be prevented from performing surgical treatment because they are not as well equipped as centres in developed countries, *provided that adequate expertise exists*; well-trained personnel can do a qualified job without the latest, most expensive technological advances.

The economic feasibility of surgical treatment in countries with limited resources is readily apparent. Data from countries such as Brazil and India show that epilepsy surgery can be performed at one-tenth or less of the cost in developed countries [5,10].

Also, it is important to understand that antiepileptic drugs (AEDs) are often unavailable, unaffordable or irregularly distributed in countries with limited resources [14]. It is clear that Third World governments are not purchasing and/or distributing adequate amounts of AEDs, and that most patients with epilepsy cannot afford to buy them. For those with medically refractory seizures – the ones taking more AEDs, and in greatest need of regular supplies – the situation is even worse. To operate successfully on some of those with medically refractory epilepsy would have an enormous, far-reaching impact on this aspect of medical care. The realistic goal to reduce or eliminate the need of AEDs in many patients should be critically considered in both the ethical and economic arguments for epilepsy surgery in developing countries [15].

Because opportunities for education and work are considerably more limited in developing countries, the handicap imposed by uncontrolled epilepsy is almost certainly greater than in areas where schooling and employment are easier to obtain. Recent data have shown that about one-half of the people who are unemployed before epilepsy surgery can find a job after operation, providing the patient does not have learning difficulties and his/her seizures are satisfactorily controlled by the procedure [16]. Psychological and social rehabilitation, however, is dependent on the preoperative educational and vocational status of the patients, indicating the need for an earlier and more aggressive approach to surgical intervention [16–19]. For non-welfare states, losing a job, or not obtaining one in the first place, can be catastrophic for the lifetime of the individual. If the cost incurred by the whole 'entourage' of the person with epilepsy is considered – money spent to travel to the doctor's office, time of caregivers off their workplaces, impossibility of caregivers holding jobs [8,20–22] – there would be an exponential beneficial effect of controlling seizures surgically. Reintegration into society, not only of the patients, but also of their caregivers [8,20–22], would justify the costs of supporting the implementation of epilepsy surgery programmes in countries with limited resources.

Surgically remediable epilepsies: conceptual advances and the impact on epilepsy surgery in countries with limited resources

The concept of surgically remediable epilepsies refers to those epileptic syndromes that are usually refractory to AEDs but respond well to surgical treatment [4]. Major advances in epileptology have had a significant impact on the feasibility of epilepsy surgery for many surgically remediable epilepsies in countries of limited resources. Technology-based research with sophisticated imaging and neurophysiological tools [18,23] resulted in a simplification of presurgical protocols in such a way that presurgical evaluation and surgical management of patients with many of these conditions can now be performed without excessive technological sophistication, provided that skilful personnel are available to identify, evaluate and operate on them.

In at least three common surgically remediable 'scenarios', technological and conceptual advances generated by developed centres translated into more practical and feasible approaches to the evaluation and surgical treatment of patients with refractory seizures: (1) temporal lobe epilepsy associated with hippocampal sclerosis (TLE/HS); (2) epilepsies due to neocortical and limbic tumours; and (3) the understanding of the relevance and simplification of surgical decisions associated with large unilateral (hemispheric) lesions in children with severe epilepsies. These advances will be briefly reviewed and their role in helping out countries of limited resources to offer surgical treatment of epilepsies will be highlighted. Situations within these broader scenarios in which a higher level of experience and

technological sophistication are still needed will also be pointed out.

Patients who have temporal lobe epilepsy associated with hippocampal sclerosis can be evaluated non-invasively, often without the need for ictal recordings

Gone are the days when major uncertainties revolved around decision-making in TLE. In the pre-MRI era, any ratio of bilateral independent interictal discharges or any deviation from classical semiology dictated the need for invasive evaluation with intracranial electrodes [24,25]. The advent of MRI made clear that bilateral independent discharges are a common finding in patients with TLE associated with unilateral hippocampal atrophy, and outcome analysis in these patients demonstrated that favourable surgical results could be obtained with unilateral resection of the atrophic mesial temporal structures despite bitemporal spikes [15,26]. This obviated the need for invasive recordings, except for very selected cases (briefly reviewed below). In addition, two more recent developments have had even more impact for streamlining the evaluation of these patients. One is the possibility to move on to surgery based upon the combination of a typical semiological description, MRI identification of unilateral hippocampal sclerosis, and interictal epileptic discharges and neuropsychology concordant with the MRI [18]. The other is the reduced need for the Wada test for determining memory reserve, which derived from extensive experience with non-invasive neuropsychological evaluation and the correlation of these non-invasive findings with MRI, results of the Wada test and postoperative memory outcomes [15].

An obvious note of caution is that extensive experience with presurgical evaluation is crucial to take advantage of these simplifications in the work-up. However, such experience can be built (and is being built) in epilepsy centres in developing countries in such a way that advances derived from extensive research in developed centres are indeed being translated into better chances for patients with epilepsy who require surgery but who live in countries of limited resources. The readier availability of pertinent literature, the fact that training in the epilepsy surgery field mimics the long-held tutoring tradition in medicine (in the sense that some or most leaders of epilepsy centres in developing countries were trained – practically tutored – by experienced epileptologists in developed centres) and the energetic enthusiasm demonstrated by emerging multidisciplinary teams in countries with limited resources all contribute to a rational and straightforward development of the field.

However, there are situations in which patients with clinically and MRI-determined TLE/HS will need a more sophisticated presurgical evaluation, either including scalp ictal recordings, the Wada test or possibly invasive electrodes. These include at least those patients with bilateral hippocampal atrophy, those in whom despite unilateral atrophy the interictal discharges predominate in the opposite side, those with discordant findings between ictal electroencephalography and MRI, and also those in whom results from non-invasive memory testing are not straightforward or are discordant with the electroencephalogram (EEG) or imaging. In addition, patients with a strong suspicion of psychogenic non-epileptic seizures may also need a more detailed presurgical work-up. The goal of this chapter is not to analyse all these situations in detail (most are indeed the subject of active current research with the benefit of technologically advanced methodologies such as functional imaging), but to highlight the fact that these are the minority of cases of TLE/HS in epilepsy centres in developing countries. Today, most patients with TLE/HS can be worked up in a simplified fashion, and this is a clear demonstration of the benefit of advances in the field that are generated by developed centres helping the treatment of patients from countries with poorer resources.

Lesionectomy plus electrocorticography-guided corticectomy can successfully treat most medically refractory epilepsies due to neocortical and limbic tumours

A never-ending debate contrasts the views of epileptologists when approaching patients with refractory seizures due to low-grade gliomas and developmental tumours. These are patients in whom seizure semiology either reflects the cortical area harbouring the lesion or well-known symptomatogenic zones activated by ictal propagation through predictable pathways. Not unexpectedly, there are indeed instances when seizure semiology is uncharacteristic or poorly indicative of a specific cortical localization. The 'focus' of debate is whether one can assume that the 'focus' (i.e. the epileptogenic zone) is contained in the surroundings of the lesion or if it should be actively probed through invasive strategies. A number of (descriptive) studies have shown that resection of the lesion combined with electrocorticography (EcoG)-guided corticectomy can lead to very good results (reviewed in ref. 27). My understanding is that opposing views (i.e. those in favour of invasive evaluations in these patients) are fuelled much more by conceptual differences than by the objectivity of better results.

As in the situation concerning TLE/HS, there are instances when one needs a more sophisticated evaluation of patients with seizures due to low-grade tumours, particularly when the lesions are located in the vicinity of eloquent motor or language cortical regions. Again, these are the minority of cases, and the clinical research entertained by different centres in rich countries suggests that in most instances presurgical evaluation can be conducted non-invasively leading to high grades of seizure control with surgery.

In children with severe epilepsies, surgical decisions associated with large unilateral lesions are usually straightforward

The work of centres of excellence in paediatric epilepsy surgery has demonstrated that epilepsy surgery in children aims both at seizure control and at unleashing motor/cognitive development [28,29]. Taking advantage of (and promoting) brain plasticity in the first years of life is crucial to an adequate management of children with severe epilepsies due to unilateral large lesions. Most of these children have one of a limited number of aetiological entities that are amenable to a simplified, objective presurgical evaluation and early surgical referral. Thus, children with hemimegalencephaly and other hemispheral malformations, Sturge–Weber disease, Rasmussen's encephalitis and large unilateral porencephalies often present with congenital hemiparesis, severe epilepsy, psychomotor retardation and a pseudoencephalopathic

EEG [30]. Understanding that these children with unilateral epileptogenic lesions must be referred to surgery despite diffuse electroencephalographic abnormalities is a crucial epileptological construct, and such knowledge should see no boundaries between countries with extensive or limited resources.

For the present discussion, it should be made clear that a very good surgeon and adequate postoperative management in paediatric intensive care units are the key elements in these cases. It really does not matter very much whether interictal spikes are unilateral, bilateral independent or generalized. When facing a child with refractory epilepsy and psychomotor slowing due to a large unilateral lesion, the lesion must be removed either through a multilobar resection or a functional hemispherectomy. There is usually no need for invasive recordings or sophisticated functional imaging studies, although in some selected cases long-term prognosis may be related to the extent, for instance, of metabolic abnormalities in the 'good' hemisphere [31]. Important issues in this scenario sometimes must be dealt with by more experienced teams. For example, some large cortical malformations may apparently spare the primary motor cortex but microscopic extension to this region is often seen. Thus, to determine the best strategy may be difficult, and reoperations are not uncommon when a more conservative approach is preferred. There are also issues related to language dominance and transfer. When dealing with children with large destructive lesions also involving language cortex, language is almost certainly transferred to the other hemisphere; however, this is not always the case with malformative lesions, for instance, and the age at operation is then most relevant in terms of anticipated language plasticity [32]. Despite intricacies involved in decision-making in some cases, the point here is that surgery is indicated in many or most cases of large hemispheric lesions in children with refractory epilepsy and psychomotor retardation, and may be planned on the basis of simplified presurgical protocols that are accessible to epilepsy centres in areas of limited resources.

How epilepsy centres in countries with limited resources are organized to offer surgery as a treatment option in epilepsy: the stepwise approach, the minimal requirements and the Brazilian experience

In general, the level of organization and expertise of epilepsy centres in countries of limited resources has not really changed in the last 10 years. What has happened, however, is that some centres have clearly upgraded their capabilities and many others have started out, naturally focusing on the simpler cases.

Stepwise approach

Before discussing the approaches for refractory epilepsies in epilepsy centres in countries with limited resources, let us briefly review the performance and the type of cases evaluated and operated upon by centres in developed countries. Of 11680 operations for epilepsy reported by developed countries throughout 1990, 7766 (66%) were anterior temporal lobectomies or amygdalohippocampectomies performed for refractory temporal lobe epilepsies. In 2000, the group at the Mayo Clinic reported their results for the 5-year period 1989–1993. At the latest count, only 210 out of 493 operated patients (42%) had achieved 1 year or more of seizure freedom at any time during the follow-up. Interestingly, almost 90% of these 210 patients (188 to reproduce the exact figure) were temporal lobe cases [33]. These results from a highly regarded institution in the USA demonstrate that there is still much room for improvement in the performance of centres from developed countries when tackling extra-temporal epilepsy patients presenting with refractory seizures.

Minimum requirements

The minimum requirements to run an epilepsy surgery programme in countries of limited resources depend upon the types of surgically remediable epilepsy syndromes that a given centre would want to approach [2]. A rational framework would be to get organized to evaluate and operate on patients presenting with the three surgically remediable epilepsy scenarios discussed above: mesial temporal lobe epilepsy, low-grade gliomas and developmental tumours, and large unilateral lesions in children. These entities are common and their presurgical evaluation is not too demanding in terms of 'requirements'. Most patients who harbour these surgically remediable epilepsies can be successfully operated on the basis of epileptological and neurosurgical expertise, scalp electroencephalography, clinical semiology, MRI and neuropsychological testing [34–43]. Thus, these are the basic requirements for an epilepsy surgery programme in countries of limited resources [1–3]. However, well-trained specialists, providing the necessary expertise, are the key. A stepwise approach to more complex epileptic disorders would then be matched by an increase in the technological capabilities at selected regional and national centres [2].

In addition, there is the obvious need to optimize the allocation of limited technological resources. In practice, this means that potential candidates for epilepsy surgery must have access to MRI and video-EEG monitoring in countries where inequalities of medical care may tend to restrict availability of costly procedures to certain strata of the population. National campaigns, with the support of the ILAE, can, and should, be promoted to rationalize the use of the necessary resources in favour of those patients who will most likely benefit from a surgical procedure (see section on the Brazilian experience, below).

The Brazilian experience

In Brazil, 1994 saw the establishment of a national epilepsy surgery programme within the public health system, sponsored and coordinated by the Health Department. This programme was created by the joint efforts of the Brazilian League of Epilepsy, the Brazilian Society of Clinical Neurophysiology and the Brazilian Society of Neurosurgery, all of which were active participants of a Committee named directly by the Minister of Health. The main objectives of this Committee were threefold: (1) to establish a nationwide epilepsy surgery programme; (2) to implement internationally accepted medical standards; and (3) to maximally optimize resources at low costs. In order to achieve these goals a two-step strategy was implemented, which included strict criteria for accreditation of epilepsy surgery centres based on minimal requirements and clearly defined guidelines for indication of epi-

lepsy surgery (temporal and extratemporal resective surgery, hemispherectomy and callosotomy).

The first 10 years (1994–2004) of the programme have proved to be highly successful in several aspects. It started out in 1994 with three accredited centres and expanded to eight centres, distributed in different geographical regions – seven connected to academic institutions that were dedicated not only to medical assistance, but also to education and research. Other emerging centres are applying at present for accreditation as epilepsy surgery centres, in an organized process led by the Health Department.

The implementation of this programme led to universal access to epilepsy surgery in Brazil, increased 13 times the annual number of epilepsy surgeries, and boosted the scientific development in the field of epileptology. Moreover, the programme encouraged a network of centres with full capacity to train young Brazilian professionals in epileptology, with tremendous gains in patient care at all levels, including in the surgical treatment of epilepsy.

Are minimum requirements for performing epilepsy surgery changing?

The answer to this question is 'probably not'. What is changing is the profile of patients being operated on at epilepsy surgery centres in develop*ed* countries as a result of technological advances, particularly in neuroimaging [44]. A stepwise inclusion of more and more complex epileptic conditions (i.e. broadening of the indications for epilepsy surgery) can occur both in develop*ed* and in developing countries at the same rate as refinements in the preoperative diagnostic technology. It is clear that more patients benefit with technological advances, but it is important not to hamper development of epilepsy surgery in countries with limited resources just because the latest advancements are not at hand.

Despite all the difficulties that need to be faced by those who wish to perform epilepsy surgery in developing countries, there is already a transformation in progress. Successful epilepsy surgery is a reality in many developing countries, and the number of these has increased steadily in the last 10 years [6].

A final word on education, early identification of refractory seizures and the value of epilepsy surgery

Specialized epilepsy centres in developing countries could break the cycle of intellectual and technological dependency on the industrialized world. This is a first step to generate knowledge and begin a process of good-quality training locally. Highly trained personnel are crucial to the process; this has to be taken seriously and an investment in such training – abroad or in already established centres in some developing countries – is a necessary first step. Once these epilepsy centres in countries with limited resources begin to produce good epileptologists, a 'positive cascade' may ensue, with better diagnosis of epilepsy syndromes, clearer understanding of rational ways of pharmacological treatment and increased awareness in society of the need for governmental measures to ensure epilepsy care at all levels, including the purchase and distribution of adequate supplies of the more useful antiepileptic medications. Thus, raising the set point of epilepsy care as a whole is a background goal of epilepsy surgery in countries with limited resources. Furthermore, when it becomes apparent that developing countries can generate credible original research in epilepsy, epileptologists from these regions will gain the confidence to create reliable protocols to investigate and treat patients in a manner relevant to their environment. Cost-effective, high-quality care within the (realistically) available means of each society is likely to be achieved more easily by locally generated knowledge and experience.

Recently, two seminal studies have confirmed long-held beliefs that patients with refractory seizures can be identified early in the course of the epilepsy [45] and that surgical treatment is more effective than AED treatment for patients with temporal lobe epilepsy whose seizures have been refractory to medications for some years [46]. These robust findings leave few doubts about the unfavourable evolution of patients with a number of well-defined epilepsy syndromes and the possibilities of reversing this unfavourable picture with surgery for epilepsy. There is no justification for people with epilepsy living in countries with limited resources to be excluded from the benefits of epilepsy surgery.

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Index

Page numbers in *italics* represent figures, those in **bold** represent tables.

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