

PHARMACOTHERAPY for CHILD and ADOLESCENT PSYCHIATRIC DISORDERS

Second Edition, Revised and Expanded

David R. Rosenberg
Pablo A. Davanzo
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Second Edition, Revised and Expanded

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Series Introduction

Children have been the orphans of American health care. In a system dominated by the politics of who will pay the bills, those without votes get short shrift. Thus we have Medicare rather than Pedicare, and millions of Americans without either health insurance or other means of paying for care. While some communities have an adequate safety net, most do not. In the absence of funded care, drug companies have seen little reason to invest in the necessary and difficult task of evaluating the safety and efficacy of drugs in the treatment of children. Until recently, guesswork and “clinical judgment” were the only guides to medicating children suffering from major depression or anxiety. Fortunately, pressured by pediatric groups and children’s advocates, the National Institutes of Health recently mandated the inclusion of children in clinical trials unless contraindicated, and Congress has attempted to induce drug companies to participate by granting an additional six months of patent protection when they have determined the appropriate dosing for children.

Another major problem affecting children has been the relative absence of clinical research. They are not merely small adults but have a complex evolving development, a changing physiology and (psychology), and often different clinical expressions of the same pathology. Proper diagnosis requires understanding the ever-changing child in his or her life context. Young investigators and new,

less invasive techniques are leading to an exciting growth in knowledge about the pathophysiology of childhood illness.

The editors of this volume have brought together an impressive group of experts who have been able to summarize what we know—and what we can only guess at but need to know—and who are able to make it all clear. Importantly among the chapters is one on the ethical issues of research in children, a reassurance to all.

I would like to add a special tribute to Dr. Samuel Gershon. After America's disastrous experience with lithium as a salt substitute for patients with hypertension, there was reluctance to use this "dangerous" compound in the treatment of psychiatric patients. Dr. Gershon helped to change that attitude with his eloquence, data, and his many students. He has remained in the forefront of pharmacology among the first to study geriatric pharmacotherapy and now well ensconced in the world of children. Our profession owes him much.

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Foreword

The second edition is a timely contribution to this rapidly developing field as new therapeutic opportunities become available. In assessing the factors currently driving research, it appears that several factors are primarily responsible. There has been an increased emphasis on developmental aspects in making childhood and adolescent diagnoses. This is particularly true as the time for DSM-V grows nearer. Improved assessment procedures and better recognition of symptom clusters and functional impairment have increased intervention, consequently, exerting pressure on the pharmaceutical industry to provide new drugs for children and adolescents. Furthermore, the growth of advocacy and family groups pushing for more studies, which may even involve randomized clinical trials, is a new issue. Such developments are increasing the need for improved psychopharmacological training for clinicians.

Drs. Rosenberg, Davanzo, and Gershon have improved and expanded the first edition, enabling both clinicians and students to find in one place a comprehensive and essential set of guidelines for psychopharmacological intervention in childhood and adolescent disorders. They have updated the rapidly emerging areas of interest discussed in Part I and expanded the discussion of ethical issues, as well as pharmacoepidemiology. In Part II the editors have added two new

chapters to break-out serotonin-reuptake inhibitors from other novel (atypical) antidepressants. In addition, they have added a chapter on combination therapies. The book is easy to follow, user-friendly, and an invaluable resource for clinical specialists, regardless of discipline, who are involved in the diagnosis and treatment of child and adolescent psychiatric disorders.

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Foreword

It is generally acknowledged that psychiatry as a medical discipline has been late in embracing evidence-based medicine, and there seems to be little debate that child psychiatry has been the slowest discipline in adopting this model. There are many reasons for this, ranging from historical tradition to ethical issues in research involving children. Nevertheless, if we are to provide children with the best treatment of psychiatric disorders, then we must elucidate the pathophysiology of these disorders and conduct state-of-the-art placebo-controlled randomized clinical trials to measure the effectiveness of the purported treatments. This book summarizes the state-of-the-art in the field and points out the many lacunae that exist in our database concerning the treatment of childhood psychiatric disorders.

Drs. Davanzo and Rosenberg are members of a new generation of child psychiatrists unburdened by the tradition of a hierarchy in child psychiatry that required psychoanalytical training of its leadership. The editors and chapter contributors have reviewed the literature with a critical eye. There are, of course, other comprehensive textbooks of child psychiatry, but this is one of the few that succinctly reviews pharmacotherapy for child and adolescent psychiatric disorders.

There is much valuable material here for both the practitioner and the investigator. Dr. Vitiello's chapter on ethical issues in research involving children

reviews the many issues that in the past have hindered research in child psychiatry. Dr. Edwards provides an understandable review of the pharmacokinetics of psychotropic drugs that will be clinically useful. The other chapters are also invaluable. At a time when we have a veritable crisis of clinical investigators in psychiatry, particularly in child psychiatry, this volume will serve as a stimulus for residents and fellows in child psychiatry to choose research careers. In view of the increasing availability of research funds in areas relevant to child psychiatry a book such as this is needed to capture the next generation of child psychiatry investigators. I commend Drs. Davanzo, Rosenberg, and Gershon for the effort they have expended in putting together this concise summary of child psychopharmacology. The field will certainly be better for it.

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Preface

The second edition of *Pharmacotherapy for Child and Adolescent Disorders* is being published 8 years after the first edition. In the interim the field has continued to undergo considerable development and progress.

Although psychotropic medications have been a major therapeutic tool in the treatment of adults with mental illness for the past half century, the use of these agents in the treatment of children and adolescents with psychiatric disorders is as young as the patients themselves. One reason is that, until recently, specific psychiatric diagnoses were not well defined or characterized in the pediatric population. However, we now know that the presentation in children of many psychiatric illnesses is quite similar to that seen in adults. We also know that these disorders, if seen first in childhood or adolescence, are likely to respond to the same treatments that are effective in adults, with appropriate modifications.

A second reason that pediatric psychopharmacology is still very much in the developmental stages is the potency of the therapeutic agents and their potential side effects. When prescribed appropriately, these agents can do great good, restoring many incapacitated individuals to normal, productive lives. However, the appropriate administration of psychoactive medications requires training, skill, and ongoing interaction with the patient and family throughout the course

of treatment. This is particularly true for young patients, whose continuing growth and development may necessitate frequent therapeutic adjustments.

Finally, the treatment of children with medications that exert their primary action on the brain must be approached with great care for social, ethical, and legal reasons. These treatments carry the potential of great benefit but also carry the risk of some harm. The controversy surrounding the use of psychostimulants to treat children with attention-deficit hyperactivity disorder has brought home the lesson that the administration of psychotropic agents to children is ground that must be trod slowly and carefully.

We now have had approximately 50 years of experience, however, in administering these drugs to adults, as well as limited experience with children, and their therapeutic efficacy and associated risks are well characterized. Medications with more specific indications and fewer side effects are on the market or in the pipeline. Many investigators, particularly those who have come of age in the era of pharmacotherapy, feel comfortable exploring the use of these agents through controlled clinical trials with child patients, and more clinicians, faced with a child in psychological distress, are willing to consider their careful clinical use. Although the picture is by no means complete, we felt that enough sound information and clinical experience were now available to enable us to present the second edition.

Major changes have occurred in several key areas that have increased the role of pharmacotherapy in the pediatric population. There has been a major increase in government investment in this field. Most dramatically there has been a changing pattern over the past decade and major increases in the use of all pharmacotherapies. However, the pressing debate on this topic has focused primarily on the purported increase in and/or excessive use of psychostimulants. Also, as a result of increased government support for research in this age group and new findings on the possible success of treatments for depression, there is renewed interest in the use of antidepressants.

All of these activities have stimulated us to produce this second edition. This book will serve as a practical guide to the use of modern psychiatric drugs in patients age 18 and under. Although it is written primarily for the prescribing psychiatrist, the book can be used by other health care professionals involved in the management of children and adolescents with major psychiatric disorders, including psychologists, social workers, therapists, nursing staff and students, medical students, pediatricians, and family practitioners. We have focused on the major classes of agents currently used in clinical practice. Those agents whose use is primarily of historic interest, such as older sedative-hypnotics, are not included.

We have delineated what is known on the basis of a critical review of controlled clinical trials as the highest standard of evaluation of pharmacotherapeutic efficacy. Since child and adolescent psychiatry continues to be plagued

by a paucity of such trials, however, where there is little systematic evidence to guide clinical decision making, we have attempted to synthesize the limited available data and to offer a proposed “best resolution” of current scientific insights into those still-developing areas of psychopharmacology. Often these recommendations are based on the best clinical judgment of the authors and the consultants in the development of this book. In other situations where little is known, we discuss necessary areas for future investigation and attempt to provide suggestions for dispensing such medications as safely and effectively as possible.

We thank the following people for their critical review of the chapters and their assistance in the production of this book: Dr. Patrick Burke of Pantano Behavioral Health in Tucson; Drs. Rohan Ganguli, Matcheri Keshavan, Neal Ryan, and Boris Birmaher of the University of Pittsburgh School of Medicine; Drs. Joseph Fischhoff and James Leleszi of Wayne State University School of Medicine and Children’s Hospital of Michigan; Dr. Karen Dineen Wagner of the University of Texas at Galveston; Dr. Graham Emslie of the Southwest Medical Center at Dallas; Dr. John March of Duke University; and Drs. Lawrence Greenhill and John Mann of Columbia University.

Samuel Gershon

Contents

<i>Series Introduction</i>	William A. Frosch	<i>iii</i>
<i>Foreword</i>	David J. Kupfer	<i>v</i>
<i>Foreword</i>	Charles B. Nemeroff	<i>vii</i>
<i>Preface</i>		<i>ix</i>
<i>Contributors</i>		<i>xvii</i>

PART I. INTRODUCTION TO PSYCHOPHARMACOLOGY

1. Historical Perspective on Child and Adolescent Psychopharmacology		1
	<i>Samuel Gershon</i>	
2. Ethical Issues in Pediatric Psychopharmacology Research		7
	<i>Benedetto Vitiello</i>	
3. Pharmacoepidemiology of Psychotropic Medications in Youth		23
	<i>Daniel J. Safer and Julie Magno Zito</i>	

xiv	Contents
4. Child and Adolescent Psychopharmacology: A Call for Pharmacoeconomics Research <i>Junius J. Gonzales and Beth Bowers</i>	51
5. Clinical Pharmacology of Psychoactive Drugs in Childhood and Adolescence <i>David J. Edwards</i>	71
6. Cardiac Side Effects of Psychotropic Medications in Children and Adolescents <i>Vikram K. Yeragani</i>	87
 PART II. CLASSES OF MEDICATION	
7. Psychostimulants <i>David R. Rosenberg</i>	113
8. Tricyclic Antidepressants <i>David R. Rosenberg</i>	169
9. Selective Serotonin-Reuptake Inhibitors <i>David R. Rosenberg</i>	223
10. Novel (Atypical) Antidepressants <i>Pablo A. Davanzo</i>	297
11. Monoamine Oxidase Inhibitors <i>Pablo A. Davanzo</i>	317
12. Antipsychotic Agents <i>Pablo A. Davanzo</i>	355
13. Lithium <i>Melissa P. DelBello and Robert A. Kowatch</i>	415
14. Anticonvulsants <i>Pablo A. Davanzo</i>	453
15. Anxiolytics <i>David R. Rosenberg</i>	489

Contents	xv
16. Adrenergic Agents in Child and Adolescent Psychiatry <i>David R. Rosenberg</i>	543
17. Atypical and Adjunctive Agents <i>Jess P. Shatkin and Pablo A. Davanzo</i>	597
18. Pediatric Psychopharmacology in the Consultation-Liaison Setting <i>John V. Campo and James M. Perel</i>	635
19. Pharmacological Treatment of Substance Abuse Disorders <i>Oscar G. Bukstein and Joseph Kithas</i>	679
20. Combination Pharmacotherapy <i>Pablo A. Davanzo</i>	711
<i>Index</i>	721

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1

Historical Perspective on Child and Adolescent Psychopharmacology

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Child psychiatry as a distinct area of study is just over a century old, developing in parallel with the psychological study of normal child development. The concept of biological psychiatry as applied to child and adolescent mental disorders is even younger (Alexander and Selesnick 1966; Parry-Jones 1989). Psychopharmacology, however, is not a new concept. In the eighteenth and nineteenth centuries, several “true” psychotropics were available. Amyl nitrite was felt to be indicated for catatonia, opium and stramonium (an anticholinergic agent) for psychosis, and cannabis for depression. Of these, opium was considered the most remarkable of cures (Feldman 1965).

Ironically, these agents and the study of other psychotropics remained the exclusive domain of medicine and neurology for many years. The concept of insanity as a spiritual and thereby nonphysical illness dominated the late eighteenth and early nineteenth centuries, perhaps contributing to the dominance of psychotherapeutic treatments. The German physician Johann Christian Reil has been credited with the first systematic practice of such therapy, and in his “Rhapsodies About the Application of Psychotherapy to Mental Disturbances” (1803),

he voiced the opinion that emotional illness could not be cured by physical treatments (Alexander and Selesnick 1966).

However, Sigmund Freud (1856–1939) was the first of the Germanic psychiatrists to successfully integrate psychotherapy into a medical community that was dominated by the experimental methods of neurologists and psychologists in Germany and France. Freud's German elder, Wilhelm Griesinger (1817–1868), was one of the first to merge psychiatry with the burgeoning field of experimental neurology, advocating that all mental illness was ultimately attributable to dysfunction of the brain. His treatments focused on proper mental hygiene and symptomatic drug treatment but disdained the "trickery" of psychotherapy (Alexander and Selesnick 1966).

The practice of psychopharmacology served, in some ways, to unite these two divergent approaches to mental illness. Prior to the 1950s, psychotropic drugs were used for nonspecific results: amphetamines and other stimulants for alertness or to alleviate depression; barbiturates and other sedatives for calming or sleep. Chlorpromazine was developed accidentally by the French pharmaceutical firm Rhône-Poulenc in an attempt to synthesize antihistamines with fewer side effects (Jacobsen 1986). Its first psychiatric use in 1952 yielded remarkable and unexpected effectiveness for the excitement and psychosis of mania (Hamon et al. 1952). Simultaneously, the monoamine oxidase inhibitor iproniazid was used for treatment of tuberculosis and had an unexpected antidepressant effect (Seligman et al. 1952). With the discovery of these drugs, an era of specific pharmaceutical treatment for mental illness began and psychiatrists began to consider both psychotherapy and pharmacotherapy as standard treatment.

If psychiatry was somewhat slow to make use of drug treatment, child psychiatry virtually dawdled. Leo Kanner wrote the first textbook on the subject, *Child Psychiatry*, a thorough and scholarly work whose later editions were maligned for giving rise to the concept of the "schizophrenogenic mother" (Kanner 1935). The fourth edition of this 735-page text, released in 1972, devotes only two pages to the psychopharmacology of childhood disorders (Kanner 1972). Discussed are Bradley's early studies of amphetamine for the treatment of behavioral disorders (Bradley 1937; Bradley and Bowen 1941), the use of anticonvulsants for behavioral disruption (Pasamanick 1951), and several open trials of chlorpromazine for the severely disturbed (Gatski 1955; Freed and Pfeifer 1956; Hunt et al. 1956). Notably absent are clear diagnostic categories of subjects and a critique of research methods used in these studies. Kanner closed the discussion with a quote from Bender, who said: "We appear to be in the beginning of a new era of understanding the use of drugs in psychiatric practice" (Kanner 1972).

In truth, by 1972 psychiatry was already well into this new era, with child psychiatry at least a decade behind. The early reports of Bradley were replicated several times between 1937 and 1970, but only in the past two decades have researchers established specific indications, outcome measures, pharmacokinetic-

ics, and dose-response relationships for stimulant medications (see Chapter 7) (Wiener 1984). Reports of the successful use of neuroleptics in children were common between 1953 and the late 1960s, but studies were invariably performed on heterogeneous diagnostic groups using poorly controlled designs (Wiener 1984). The work of Magda Campbell and colleagues from the early 1980s to the present provided studies of neuroleptic therapy in childhood psychosis, autism, and aggression, as well as the careful analysis of the short- and long-term side effects of these drugs in youngsters (see Chapter 12). Finally, the existence of major affective illness, and therefore its treatment, in prepubertal children was not widely accepted until the late 1970s and was pioneered by Puig-Antich and others (Puig-Antich 1980; Petti and Law 1982).

It is important to stress the magnitude of the problem facing this field. The Institute of Medicine (1989) has estimated that at least 12% of children under the age of 18 years, or now approximately 8 million children and adolescents in the United States, have a diagnosable mental disorder.

Some of the earliest estimates of pharmacotherapy in this age population were reported for attention-deficit hyperactivity disorder (ADHD) by Stephen and Sprague (Stephen et al. 1973; Sprague and Sleator 1973). Their estimates for public and private schools in the Chicago area during 1970–77 were 2–4%. However, reports by Safer and Krager starting in 1971 state that the prevalence of drug therapy in this population has doubled every 4–7 years, and by 1987 6% of all public elementary school students in Baltimore county were receiving medication for ADHD (Safer and Krager 1988).

This issue is still hotly debated in regard to aspects such as overuse of stimulants and overdiagnosis of ADHD in the United States and especially compared with these figures for the United Kingdom and Scandinavia. The issue of ongoing concern, however, is that findings from more recent treatment management studies suggest that many of these same problems may still be with us (Jensen et al. 1989).

A recent report by Zito et al. (2000) on the increased prescribing of psychotropic medication to preschoolers set off alarms in the daily press and in news magazines (Shute et al. 2000). A significant feature of these findings is that they focused on a population of preschoolers 2–4 years of age. In short, they found that the number of children in this age group on methylphenidate (Ritalin), antidepressants, and other psychoactive drugs increased dramatically from 1991 to 1995. They also cite a U.S. Food and Drug Administration (FDA) report that 3000 prescriptions for fluoxetine were written for children under one year of age in 1994. Also presented was a 1998 report that 57% of 223 Medicaid enrollees aged 4 years and under with a diagnosis of ADHD received at least one psychotropic medication to treat this condition.

In brief, stimulant treatment in preschoolers increased approximately threefold in the United States during the early 1990s. Also, there is a great debate

about the high use of medication to treat ADHD in the United States compared with other countries. This aspect of the debate has caused a United Nations panel to note that the United States consumes 80% of the world supply of methylphenidate. Another current medication for ADHD, clonidine, has had a dramatic increase in usage. Increased prescribing of clonidine seems to be occurring without the benefit of significant data on its usage for this indication.

The increased prescribing of antidepressants is also a major feature of the Zito report, particularly so as the efficacy of tricyclic antidepressants (TCAs) has not been shown to be effective for depression in this age group (see Chapter 8). Psychotropic drug usage in children is of such serious concern that Chapter 3 is devoted to a more thorough consideration of the enormous impact these findings have for society and for the appropriate use of these medications.

A unique situation exists in pediatric psychopharmacology the common "off-label" use of agents approved by FDA for use in adults. There are many problems with this form of medication usage in the pediatric population. A major problem is that physicians are prescribing medications for which there may be inadequate data on safety, efficacy, and appropriate dosing. Thus, there is an inadequate research database for many agents used extensively in pediatric psychopharmacology. Many efforts are currently being made by FDA, the National Institutes of Health (NIH), academic centers, and the pharmaceutical industry to seriously address these important issues. Therefore, it is very likely that the next decade will provide us with a much-improved level of scientific findings to markedly propel rationale pharmacotherapy in child and adolescent psychiatry.

Unique differences in therapeutic outcome with TCAs in children and adolescents provide a dramatic demonstration of the need for special targeted studies of psychotropic agents in this population. The clear efficacy of TCAs in adults was a reasonable justification for their study in the pediatric population with depression. A series of studies in children with a variety of these agents demonstrated no significant therapeutic benefit of this class of drugs.

A variety of reasons have been offered to explain this lack of efficacy. This question is now highlighted by reports of therapeutic efficacy of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants by Emslie et al. and others (Emslie et al. 1997). These observations highlight the special issues related to this field. For example, the diagnostic entity of depression in children and adolescents has only been defined and accepted relatively recently.

The existence of major depressive disorder in prepubertal children and adolescents has been reported in epidemiological studies (Fleming and Offord 1990). Thus, depression is now increasingly recognized in this age group, and there is an increase in the rate of depression and a decrease in the age of onset (Klerman and Weissman 1989; Shaffer et al. 1988). A similar development in diagnostic classification has also occurred with bipolar disorder in this population, opening up pharmacotherapeutic possibilities for another segment of this undertreated population.

In reading this textbook, it may become apparent that definitive studies of most psychopharmacological approaches to child and adolescent mental illness have yet to be performed. It is the authors' hope that a critical review of current knowledge in this area will prove useful to practicing physicians and serve to highlight the limitations of our current knowledge in pediatric psychopharmacology. Similarly, it is the authors' opinion that the treatment of child and adolescent mental illness, both pharmacological and nonpharmacological, represents the highest priority for new research and funding.

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2

Ethical Issues in Pediatric Psychopharmacology Research

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INTRODUCTION

Attention to ethical aspects of research is essential when conceiving, designing, and conducting biomedical investigations in humans (DHHS 1991a). Research involving children and adolescents is subject to additional requirements because these subjects are considered a “vulnerable population,” not able to make fully informed decisions about participation in clinical investigations (DHHS 1991b). It is probably not coincidental that one of the first chapters of this book on pediatric psychopharmacology is devoted to bioethics. In fact, without careful integration of ethics into science, clinical investigation is not possible.

Research in pediatric psychopharmacology is justified by the need to establish the efficacy and safety of psychotropic medications that hold potential therapeutic value for youths suffering from psychiatric disorders. Experience has taught that efficacy and safety of medications cannot be solely inferred from

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studies conducted in adults (Vitiello and Jensen 1997). Because denying children the benefits of knowledge about potentially effective drugs would be unethical, research remains the only reasonable alternative to a perennial state of ignorance.

The main ethical principles of pediatric research have remained substantially constant over the years, but there has been an ongoing process of interpretation, refinement, and implementation of these principles that has made of bioethics a lively and dynamic discipline (Hoagwood et al. 1996). Recently, the general awareness of the critical importance of human subject aspects of research has increased, as also reflected in the interest of the media and lay public in these issues. A number of conferences and workshops have been held on ethical aspects of mental health research (Arnold et al. 1995; Shore and Hyman 1999; Charney 2000). In 1998, the National Bioethics Advisory Commission published the report “Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity” (NBAC 1998). In 1999 the National Institute of Mental Health (NIMH) formed a work group of the National Advisory Mental Health Council with the task of further reviewing the human subject aspects of grant proposals that include discontinuation designs or nontherapeutic challenges. In 2000 the National Institutes of Health (NIH) issued new requirements for documenting the education of clinical investigators in the protection of research subjects (NIH 2000). These and other activities attest to the prominence of ethics in designing and conducting clinical research (Hoagwood et al. 1996).

This chapter is intended as a general introduction to the bioethics of pediatric psychopharmacology but cannot exhaustively address all the complexities that specific studies may entail. The researcher is required to keep abreast of the state-of-the-art of bioethics by following the relevant literature, as this discipline is, like medicine itself, in constant evolution.

GENERAL PRINCIPLES

Research in pediatric psychopharmacology is regulated by the ethical principles of human research with the addition of other requirements that are specifically relevant to research in children. “Children” are here defined as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted” (DHHS 1991b). Thus, the upper limit of the definition of “child” varies according to state laws and social context. For instance, adolescents who are married, have become parents, or serve in the military may be considered “emancipated” based on local laws. For research funded or regulated by the U.S. federal government (e.g., studies supported by NIH grants or contracts or conducted under an Investigational New Drug application to the Food and Drug Administration), the ethical principles are codified in specific rules for hu-

man biomedical research in general (DHHS 1991a) and in children in particular (DHHS 1991b). In fact, this policy sets the standard also for most nonfederally sponsored research and is often referred to as the “common rule” of clinical research. According to these rules, the main general requirements of research in children are that: (1) the research protocol and consent forms must be approved by an Institutional Review Board (IRB), (2) informed *permission* must be obtained from the parent (or other legal guardian) and *assent*, when possible, from the child, and (3) the benefit-risk ratio must be favorable to the child (at least as favorable as the available alternatives). The characteristics of the proposed research determine which further conditions apply. If participation in the study is expected to directly benefit the child, the benefits must outweigh the risks involved in the study. In other words, the benefit-risk ratio must be favorable to the child. For “benefit” it is meant an identifiable improvement in health condition that is anticipated or expected. Treatment studies generally fall into this category. If, on the contrary, the research in question does not have the potential to directly benefit the study participants, further considerations apply. If the study is not relevant to the condition of the research participant, the child cannot be exposed to procedures or interventions that entail more than *minimal risk*. This rule applies to research involving normal children who neither suffer from a disorder nor are at increased risk for developing one. However, if the study is relevant to the child’s illness or condition and is expected to generate new knowledge of “vital importance” for the understanding or amelioration of the child’s disorder or condition, exposure up to a *minor increase over minimal risk* can be allowed. Figure 1 summarizes these different situations. In exceptional situations, research not otherwise approvable under these criteria can be conducted if the Secretary of Health and Human Services in consultation with a panel of appropriate experts has determined that it presents an opportunity to advance the understanding, prevention, or treatment of a serious health problem of children. But this last option has been seldom used.

The interpretation of these criteria hinges on the concepts of *minimal risk* and *minor increase over minimal risk*. In general terms, minimal risk is defined as risk for harm not greater than ordinarily encountered in daily life or during routine physical or psychological examinations or tests (section 46.102(i) in DHHS 1991a). Thus, minimal risk does not equal “no risk.” There is, however, no uniform agreement on the boundaries of minimal risk. The interpretation and application of this general definition to specific research projects varies across settings and Institutional Review Boards (IRBs). Even more variable can be the interpretation of minor increase over minimal risk, and this can well contribute to the relative heterogeneity of IRB decisions. It must be pointed out that the federal regulations establish that research without a direct benefit to the child and involving a minor increase over minimal risk can be considered only if (1)

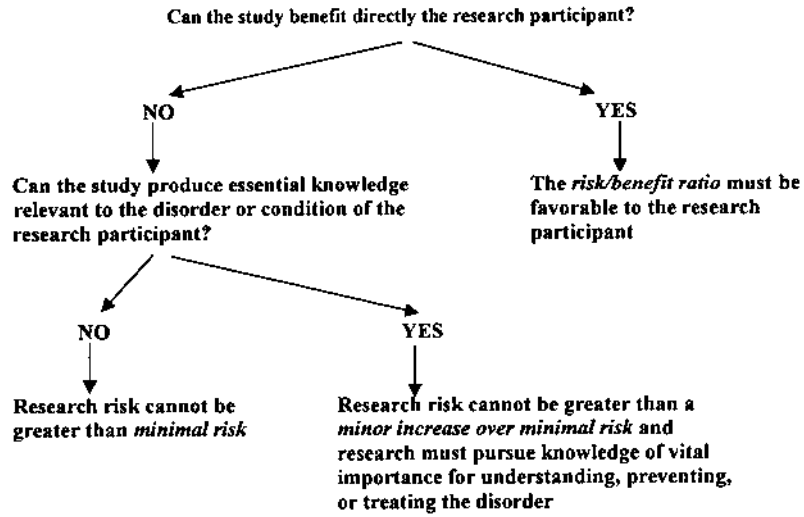


FIGURE 1 Basic decision tree about pediatric research. (From Code of Federal Regulation: Title 45, Part 46: Protection of Human Subjects, DHHS 1991. Also available on the Web site of the Office for Human Research Protections (OHRP) at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>)

it presents “experiences to the subjects that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations” and (2) the study has the potential to generate new knowledge considered of “vital importance” for understanding or treating the child’s disorder or condition. When possible, permission for this type of research should be obtained from both parents.

Most research in pediatric psychopharmacology offers a potential therapeutic value to study participants, and it is therefore regulated by the benefit-risk ratio. The concepts of minimal risk and minor increase over minimal risk are relevant to nontherapeutic drug administrations with the purpose of elucidating mechanisms of action, pharmacokinetics, or pathogenesis of illness. As described, these studies do not carry an anticipated direct benefit to participants, but may be ethically acceptable if (1) they entail no more than a minor increase over minimal risk, (2) essential knowledge can be gathered on the disorder in question, and (3) children participating in the research suffer from the disorder or are at increased risk for it (Figure 1). Thus, studies of pharmacokinetics and drug metabolism can be generally considered in children who suffer from the disorder and are treated with the medication to be studied.

TREATMENT STUDIES

Research that presents greater than minimal risk but also the prospect of direct benefit to the child is justified if the prospective benefit outweighs the potential harm (section 46.405 in DHHS 1991b). The critical threshold for deciding the ethics of a treatment study is the benefit-risk ratio. In determining this ratio, consideration is given to such elements as severity of illness, availability of established effective and safe treatments, and anticipated efficacy and safety of the experimental treatment. Clearly, for the study to be acceptable, the medication being investigated must have the potential to improve the child's condition with acceptable risks. In addition, attention must be given to the choice of comparison group and experimental design.

Ethical Issues Related to the Choice of Comparison Groups in Clinical Trials

Various types of comparison groups can be considered in child psychopharmacology, such as the use of alternative active treatment (pharmacological, psychosocial, or combined), placebo, or referral to usual community treatment ("treatment as usual"). Of these, the choice of an alternative active treatment is the least likely to raise ethical concerns, since all the study participants are expected to receive potentially active interventions. However, it may not be experimentally informative to compare directly "active" treatments, unless their efficacy and safety have already been proven in previous trials and the aim of the present study is to show superiority of one treatment over the other. In fact, in the absence of a differential treatment effect, it may be impossible to prove equivalence without the presence of a placebo arm to ensure the internal validity of the experiment (Leber 2000; Miller 2000). The use of placebo remains the object of much discussion both from an ethical and scientific point of view, as also shown by the large literature addressing its use in medical research in general and in psychopharmacology in particular (Rothman and Michels 1994; Taubes 1995; Weijer 1999). While a complete examination of the various aspects involving placebo is beyond the scope of this chapter, certain considerations are inevitably relevant to pediatric psychopharmacology research. One approach to the appropriateness of placebo in a given study is to examine the available alternatives to placebo. Which treatment can the child receive in clinical practice if he were not to enter the study? If no treatment or only interventions of questionable efficacy and safety are available, the use of placebo is easy to justify. In fact, few efficacy and safety medication trials have been conducted in children, and the body of literature in this field is markedly smaller than in adults. Since it would be erroneous to infer efficacy and safety of pharmacological treatments in children based only on data collected in adults, it is generally easier to find " equipoise " in a placebo-controlled trial

in children than in adults. In a study comparing two or more treatment conditions, “equipoise” is defined as situation of uncertainty in the scientific community as to the relative efficacy of the conditions being tested (Freedman 1987). If, on the other hand, treatments of proven efficacy and safety are available to children, the potential risks of receiving placebo need to be carefully weighted against the value of developing, through research, potentially superior treatments for the child’s disorder. Placebo does not equal “absence of treatment,” rather it is absence of “specific” treatment. In conditions such as child depression, the placebo response rate is about 35–40% and can be as high as 60–70% (Puig-Antich et al. 1987; Birmaher et al. 1999), which compares to an average response rate to active medication of 55–60% (Emslie et al. 1997). If exposure to placebo is scientifically necessary, limited in time, unlikely to lead to detrimental consequences, and carefully monitored for possible emergence of unwanted clinical developments, a placebo-controlled study is easier to accept from an ethical point of view. This has been the case for short-term clinical trials in children with depressive disorder or attention deficit hyperactivity disorder (ADHD) (Emslie et al. 1997; MTA 1999).

In placebo-controlled trials, the adoption of certain procedures can minimize risk and improve the benefit-risk ratio. It is essential to describe in detail the specific risks and available alternatives in the consent/assent forms. In addition, it has become standard practice to offer, at the end of the placebo-controlled study, open-label active treatment to those patients who have not improved while on placebo. This procedure ensures that all patients, including those randomized to placebo, are eventually offered active treatment. In parallel, it has become more common to “break the blind” individually of each patient after he or she has completed the blinded study, rather than to wait for all the patients to have completed the clinical trial. A prompt feedback on the treatment received in the study can contribute valuable information to the process of deciding future individual courses of treatment.

The use of subtherapeutic medication doses as a control group in lieu of a placebo poses more ethical problems than the use of placebo itself. In fact, the deliberate administration of less than effective doses of treatment can be considered ethically unacceptable, especially since this approach would expose participants to the risk of adverse events without therapeutic benefits.

“Treatment as usual” (TAU), too, can raise ethical issues. Children randomized to this condition are carefully evaluated, found to suffer from a specific disorder, and referred back to their community to receive whatever treatment is available. In fact, TAU can be quite variable in type, intensity, and overall quality. In extreme situations, because of financial difficulties or other practical barriers to accessing treatment, TAU becomes in fact a proxy for “no treatment.” In situations where there is already evidence that TAU is a substandard treatment,

its inclusion in a research protocol is ethically difficult to justify (and also of limited interest from a scientific point of view). When TAU is deemed acceptable, some sort of patient monitoring by the researchers is usually needed to ensure that the possible emergence of serious symptoms during TAU receive appropriate attention and care. Patients randomized to TAU are “research participants,” who perform an essential role by contributing data towards addressing the research hypothesis. Still, their treatment is not managed by the researchers, but by community clinicians. The protocol and consent forms must specify the responsibilities of the investigators vis-à-vis those of community clinicians. For instance, when patients in the TAU are periodically assessed by the research team for collection of clinical data, new information relevant to the treatment of these patients and their safety (e.g., suicidal ideation, abuse) may emerge that needs to be shared with the treating clinicians and child protection agencies.

Ethical Issues Related to Special Experimental Designs

Among research designs, the “discontinuation design” must be carefully examined for human subject protection. This design is typically adopted to test the therapeutic value of continuing treatment as compared to discontinuing it. This type of question can be clinically important. How long should patients continue receiving treatment after they have fully recovered from the acute episode of the disorder? In psychiatry, pharmacological treatments are seldom curative and disorders are often chronic or tend to recur. In these cases, does the prophylactic administration of medication reduce the risk of recurrence? Prolonged use of medications may be associated with the emergence of toxicities or unfavorably impact development in children. Does the benefit of continuing treatment outweigh the long-term side effects? The value of continuous long-term treatment in preventing recurrence of various disorders, such as depression, has been proven in adults (Kupfer et al. 1992; Keller et al. 1998). These studies have utilized a discontinuation design: patients who had responded to medications were randomly assigned to continuing treatment or switching to placebo. At this time, our knowledge of treatment effects in children is mainly limited to short-term studies, usually lasting no longer than 2–3 months. The potential value of continuing treatment must be considered against the risks of long-term exposure of children to treatments without empirical support for their efficacy and safety. Moreover, the course of most psychiatric disorders is not well defined or predictable in the young. Because of the developmental changes that occur and their variability across individuals, it is possible that symptoms attenuate with time or become more easily managed to the point that continuous administration of medications may be unnecessary. For these reasons, a discontinuation design can be warranted in certain disorders and with certain medications. If a discontinua-

tion design is adopted, however, it is essential that the consent/assent document be clearly informative and descriptive of the potential risks of discontinuing treatment. If the discontinuation trial is only one phase of a larger study including an initial treatment phase, a new consent should be obtained from the patient and family when transitioning from the treatment to the discontinuation phase. Potential research subjects must be informed that many clinicians would maintain drug responders on treatment rather than stopping medications and that subjects need not enter this next phase. What is known about rates of relapse or exacerbation should be provided along with the specific symptoms and information about the possible detrimental impact on school, work, and social functioning, including the legal consequences of abnormal behavior. Thus, study participants and their families should know “what to look for” should an exacerbation occur, and a system of prompt intervention should be in place in order to identify possible relapse as soon as possible and treat the patient accordingly. Interim analyses and review of the data as they accrue in the study are often necessary to verify whether the relapse rate has been significantly greater among the patients who discontinued treatment. To preserve the blindness of the trial, these interim analyses are usually reviewed by the study Data and Safety Monitoring Board (DSMB), a panel of independent experts who can become “unblinded” to random assignments.

A different type of treatment “discontinuation” occurs when patients undergo “wash-out” of medications before an examination or a test that must be conducted in a drug-free condition or before entering a treatment study of other medications. A wash-out may be warranted if the efficacy or safety of the treatment is questionable or if potentially superior treatments are available. This procedure is, however, problematic if the treatment has been clearly effective, the purpose of the wash-out is to acquire research data that do not carry a direct benefit to the child, or the discontinuation is likely to result in a recurrence of significant symptomatology. Only if the results of the proposed study are likely to fill an important knowledge gap should one proceed further and consider the balance between risks to the participants and benefits to the field. In some situations, the temporary discontinuation of psychotropic medication is not likely to result in any significant risk or disruption of functioning for the child. For instance, the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA 1999) compared medication to psychotherapy and combined treatment; children were evaluated at baseline off medications and, if they had previously been on medication (usually methylphenidate or other stimulants), they were taken off before the assessments. The risk of discontinuing treatment was considered low, given also that the total time off medication was kept to an absolute minimum in order to avoid any untoward effects on home and school performance and close contact was maintained between the study case manager and the referring physician.

A particular situation that requires extreme alertness to human subject protection is that found in the so-called nontherapeutic challenge studies. In these protocols, a pharmacological agent is utilized not to treat a disorder or symptoms, but to elicit a behavioral or symptomatologic response that is relevant to better understanding normal functioning, pathogenesis of mental illness, or mechanism of action of the drug. There is no direct benefit to the research participant, while there can be risks associated with the procedures. Challenge designs are often problematic and have received much attention lately (Shore and Hyman 1999). According to the federal regulations on human research, this type of research cannot be done in normal children if more than minimal risk is involved (DHHS 1991b). In most cases, nontherapeutic administration of a pharmacological agent would be viewed as more than minimal risk. If the study is conducted in children who suffer from a disorder or condition relevant to the research in question, the study can be considered if it does not entail more than “a minor increase over minimal risk” and there is a prospective of acquiring essential scientific knowledge that will advance the understanding and treatment of the disorder or condition (DHHS 1991b). NIMH grant applications for research involving discontinuation or nontherapeutic challenge designs are currently subject to an additional level of review and scrutiny by the National Advisory Mental Health Council.

CONSENT/ASSENT FORMS

For pediatric research, written informed consent (or permission) is required from an adult who has the legal responsibility for the child. In addition, if allowed by the child’s mental age and clinical condition, the concurrence (assent) of the study participant must be obtained. Children 7 years of age and older can usually provide informed assent. Assent can be verbal or, preferably, written. Consent and assent documents must be written in clear, easily understandable language that is developmentally and culturally sensitive, avoids scientific jargon, and explains technical terms. These documents must contain certain essential elements, including information about:

1. The experimental nature of the study, which is different from individualized clinical care.
2. The research procedures, frequency of contacts, and level of involvement required of the child and family.
3. Anticipated benefits that can accrue to the child.
4. Foreseeable risks that the study entails; risks include not only possible medication side effects or toxicities, but also possible lack of improvement especially if there is a placebo arm.
5. Possible alternatives to study participation in terms of available treatments that can be obtained outside the research protocol; alternatives

must be explained in detail; individualized treatment should be mentioned as an alternative.

6. The right of the study participants to withdraw from the research protocol at any time and consequences of withdrawal for continuity of care.
7. The procedures in place for protecting the confidentiality of personal data that will be collected in the study and situations when confidentiality can be overruled (e.g., presence of suicidal or homicidal urges or intentions, sexual or physical abuse).

Proper consent/assent forms are critical in clinical research. It should be noted that these documents should inform about expected benefits that can accrue to the participant and about the foreseeable risks participation in the study can entail (Shore 1996). This means that only benefits that can be reasonably anticipated should be mentioned, while remotely possible benefits, not likely to occur, are not relevant to the consent process. On the contrary, when informing about risks, all the foreseeable risks involved in research participation must be disclosed. Exceptionally rare events are not generally considered foreseeable, but those within the range for which forecasts are possible may be (Shore 1996). Consent and assent forms must be approved by the Institutional Review Board where the study is to be conducted. IRBs must include experts in the research, clinical, ethical, and legal aspects of the study being reviewed. At least one member of the IRB must not be affiliated with the institution where the research is to be conducted. Federal regulations mandate an annual review of the study progress and consent/assent forms. If new information relevant to the risk-benefit ratio of the study becomes available, these forms must be revised and updated. Likewise, if new treatments are introduced for the condition under study, the “Alternatives” section of these documents may need to be revised and updated to remain fully informative.

REIMBURSEMENTS TO STUDY PARTICIPANTS

Participation in research often requires commitment of a considerable amount of time from patients and families. Assessments can be lengthy and frequent. It is not uncommon for participants to spend many hours in the collection of research data that would not be necessary for routine clinical care. It seems only fair to reimburse research participants and their families for the time devoted to mere research procedures, in addition to transportation and parking expenses. Financial compensation for time and expenses should be appropriately modest to avoid the risk of unduly enticing patients into research protocols through monetary compensation. Payment for research participation is commonly accepted in the case of normal adults, but its use in children is problematic, unless the research procedures do not entail more than minimal risk.

DATA AND SAFETY MONITORING BOARDS

A DSMB is a committee of appropriate experts who are independent of the investigational team and, while the clinical trial is in progress, periodically review the research data with the purpose of ensuring that the trial continues to meet the safety standards. Typically, each DSMB includes several members with specific expertise in the research to be monitored and at least one statistician. It is important that the DSMB members are separate and independent from the study investigators. In this way, the DSMB can review unblinded data and interim analyses, without compromising the blindness of the researchers. The DSMB has the power to make important decisions, such as prematurely terminating a protocol that has reached a toxicity or efficacy endpoint. Interim analyses can indicate that one of the treatments under investigation is associated with unacceptable side effects or that the primary research questions can already be addressed with the data so far collected, without waiting for the completion of the originally planned sample. DSMBs have become an essential and necessary component of multisite clinical trials in order to ensure an acceptable benefit-risk ratio for research participants. DSMB reports must be made available to each study IRB, as mandated by NIH regulations (NIH 1999a).

TRANSITION OF RESEARCH PARTICIPANTS TO INDIVIDUALIZED CLINICAL CARE

An important and ethically sensitive aspect of a research protocol is the plan for transferring patients from investigational treatment to personalized clinical care at the end of the study. This phase is particularly important in the case of patients who have not improved during the study, have developed new symptoms, or have prematurely discontinued the experimental treatment. In these cases, there is a general obligation of the researchers to provide emergency treatment, stabilize the patient's condition, facilitate the transfer to a personal clinician, and ensure continuity of care. In some studies, patients who drop out of the experimental treatment continue to be assessed prospectively as part of the research project, while their clinical care is provided outside the study. Protocols should specify termination endpoint criteria for individual patients and indicate who will be in charge of the clinical care of study participants should they discontinue the experimental treatment. As already mentioned, in placebo-controlled trials it has become common to offer a course of active treatment to patients who have been assigned to placebo and have not improved. This postrandomization, open-label treatment is provided at no cost to the patients. It has also become common to let each patient know about the type of treatment she or he has blindly received at the end of the double-blind phase without waiting for the completion of the entire study. This practice provides prompt feedback that can be useful to the

patient and her or his personal physician in planning future treatment. The possible threat to the blindness of the study can be handled by maintaining the investigators “blind” to individual treatment assignments throughout the study and let another clinician not involved in the conduct of the research deal with the patients once they complete the double-blind phase.

A STEP-WISE APPROACH TO EXAMINING BIOETHICS

Clinical research requires integration of scientific and ethical considerations. Research in humans should only be considered when the research question is important and relevant to ultimately improving health. In examining the ethics of research proposals, certain aspects must be systematically reviewed. The following approach is offered as a summary of what has been discussed so far in the chapter.

When reviewing a research protocol, the following elements are sequentially examined:

1. Experimental Questions/Aims:
 - Important?
 - Relevant to clinical care?
 - Likely to advance understanding of pathogenesis?
 - Likely to advance health?

The answer to at least one of questions above should be positive. If this is not the case, the study should not be further considered.
2. Anticipated/Expected Benefit to the Research Participants:
 - Direct benefit to participants? (i.e., do they benefit as research subjects?) → Proceed and focus on the benefit-risk ratio.
 - No direct benefit, but participants suffer from a disorder/condition for which the study is relevant? If so, will the study generate essential new knowledge that is relevant to the disorder/condition? → Proceed and examine if there is greater than a minor increase over minimal risk (see Fig. 1).
 - No direct benefit and study is not specifically relevant to participants. → Proceed and examine if there is greater than minimal risk (see Fig. 1).
3. Foreseeable Risks to the Research Participants:
 - What are the risks of participating?
 - How do research risks compare to risks from alternative standard treatment/management?
4. Benefit-Risk Ratio:
 - Favorable to the research participant?
 - Which procedures can be adopted to improve it? → Additional safeguard as needed.
5. Experimental Design and Methods:

- Best compromise between risks and benefits? What are the alternatives?
- Adequate plans to promptly identify toxicity and treatment failures?
- Will a DSMB monitor the ongoing progress of the study?
- 6. Consent/Assent Forms:
 - Clearly written and understandable?
 - Include all the essential elements?
 - Make clear that it is a research study?
 - Explain the study procedures?
 - Inform about risks?
 - Inform about alternatives?
 - Inform about data confidentiality and its limitations?
 - Explain that consent can be withdrawn at any time?
 - Are forms going to be revised should new relevant information become available?

RESEARCH IN BIOETHICS

It is unfortunate that too little research has been conducted on certain aspects of clinical trials that are relevant to human subject protection. How effective are consent and assent forms in informing research participants? How could these documents be improved? How effective is the whole process of obtaining consent/assent as administered by investigators? How was the research experience perceived by the children who participated? Does placebo administration have negative health consequences for the participants after the study? How effective are the confidentiality procedures in preserving privacy of sensitive information? These are just a few examples of questions that can be addressed through research. In 1999 the NIH issued two program announcements to invite research grant applications on ethical aspects of human studies (NIH 1999b, 1999c). Some research activity in adult psychopharmacology has indeed occurred. Recently, researchers have looked at the possible association between exposure to placebo during clinical trials and subsequent suicidal behavior and found that placebo does not increase the risk for suicide or suicidal attempt (Khan et al. 2000). Thus far, research on ethical issues in child psychopharmacology has been practically absent. Still, its importance cannot be overstated. Research in bioethics is one of the most powerful means of improving our clinical trial methodology. For a list of bioethics websites, see Table 1.

CONCLUSIONS

Research in pediatric psychopharmacology is needed in order to develop effective and safe treatments. Data collected in adults are not always applicable to children, and direct participation of children in research is necessary. Many medications

TABLE 1 Bioethics Resources on the Web

Bioethics and the National Institutes of Health: http://www.nih.gov/sigs/bioethics/
Office for Human Research Protection: http://ohrp.osophs.dhhs.gov/
Research on Ethical Issues in Human Studies (NIH Program Announcement PA-99-079, March 31, 1999): http://www.nih.gov/grants/guide/pa-files/PA-99-070.html
Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (NIH Guide, June 11, 1999): http://www.nih.gov/grants/guide/notice-files/not99-107.html
Tutorial on the Protection of Human Research Subjects: http://ohsr.od.nih.gov/
Training Program in Bioethics for Investigators: http://www.centerwatch.com

are currently used in the community to treat youths with psychiatric disorders without adequate data about their safety and efficacy. Conducting research in children requires attention to specific ethical and regulatory factors, in addition to the general rules for human research. In deciding whether minors can participate in a study with anticipated direct benefit to the research subjects, the most important variable to consider is the balance between the expected benefit and foreseeable risk in the context of the severity of the child's condition and the available alternatives to the study procedures. The use of appropriate safeguards, such as frequent clinical monitoring, can improve the benefit-risk ratio. Careful attention to the consent/assent forms and to study structure and procedures, such as the presence of a DSMB, improves the benefit-risk ratio. Discontinuation and nontherapeutic symptom challenge designs can present special risks and require careful scrutiny. Since clinical trials often last several years, each study must be monitored and reevaluated to make sure that it meets the scientific and ethical standards. Research on human subject issues and protections in pediatric clinical trials is needed to guide future efforts to improve the methods and ethics of research in children.

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3

Pharmacoepidemiology of Psychotropic Medications in Youth

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INTRODUCTION

Treating the emotional and behavioral disorders of youths with psychotropic medication was very uncommon until the mid-1960s. It followed on the heels of a decade of increasingly successful psychotropic medication treatment of adults for depression and psychosis. Another major impetus to medicate youths with psychotropic agents came from repeated, double-blind, placebo-controlled research on methylphenidate and dextroamphetamine in the 1960s showing the beneficial impact of these stimulants on the classroom behavior of hyperactive children.

During the last three decades, medication treatments for attention-deficit hyperactivity disorder (ADHD) has dramatically increased. The number of youths receiving stimulant medication in the United States was estimated at 300,000 in 1974, 410,000 in 1981, 515,000 in 1979, 700,000 in 1976, 750,000 in 1988, 1.5

million in 1995, and 2.5 million in 1998 (Safer and Krager 1988; Safer et al. 1996; Safer and Malever 2000).

The rise in the number of other psychotropic drug classes for the treatment of youth has been even more dramatic. In two state Medicaid databases documenting psychotropic medication treatment for youths under age 20 from 1987 through 1996, the prevalence of α -agonist compounds rose 15- to 53-fold and that of antidepressants rose 4- to 10-fold (Zito et al. 1999a). These trends, reflecting the overall dramatic increase in psychotropic medication treatment for youths, have raised concern in the media and clearly merit more systematic study.

Coincident with these medication utilization trends, pharmacoepidemiology has been developing to apply epidemiological methods to large datasets so as to systematically report the extent and patterns of medication use in community-based settings (Hartzema 1991; Strom 2000). This chapter consequently will document and describe recent prevalence findings, trends, and factors that influence the use of these drugs in children and adolescents. It will focus mainly on the leading psychotropic medication groups prescribed for children: stimulants, antidepressants, α -agonists, and neuroleptics. (Since some reports group medication not by class but as ‘‘medication for ADHD,’’ the reader can assume that the medication referred to for ADHD is at least 95% stimulants unless otherwise noted). Because of its frequent use of late, a brief section will focus on concomitant medication treatment of youths. For further details on the issue of pharmacoepidemiology related to children with emotional disorders, the reader is directed to a recent review of medication for ADHD (Safer and Zito 2000), an earlier literature review (Zito and Riddle 1995), and a review of medication prevalence by diagnostic classification (Gadow 1999).

STIMULANTS

Types of Medication Prescribed for ADHD

Methylphenidate accounts for most of the stimulant treatment for attention problems in the United States. Marketing data from 1995 stimulant sales had the following distribution: methylphenidate (83%), dextroamphetamine (9.2%), and pemoline (7.8%) (Batoosingh 1995). Pemoline sales dropped beginning in 1997 after the manufacturer made known the drug’s risk of serious liver toxicity (Safer et al. 2001). Between 1996 and 2000, dextroamphetamine and a mixture of four amphetamine salts have vastly expanded their market share (IMS America 2000) such that the share of methylphenidate within the total for stimulants approved for ADHD dropped by 1998 to 69% (IMS Health 1998).

Another development in the United States, particularly during the 1990s, was the increasing use of nonstimulant medication for ADHD. These medications are not commonly identified in ad hoc school surveys and include drugs such as risperidone, divalproex, bupropion, and desipramine.

Prevalence Estimates of Youths with a Diagnosis of ADHD Receiving Stimulant Treatment

Point Prevalence

Using 1989 through 1996 data from a national, random-sampled survey of visits by youths to non-federally employed, office-based physicians, Zito and coworkers reported that 77% of the youths seen by physicians in 1996 and given a diagnosis of ADHD were prescribed stimulant medication (Zito et al. 1999b). In contrast, there has been a far lower rate of stimulant treatment for children identified to have the features of ADHD through check-list ratings by elementary school teachers. In such school-based studies in 1993–94 and 1994–95, only 15–26% of youths so identified were receiving stimulant medication (Wolraich et al. 1996, 1998). In community epidemiological studies in 1981–82 and in 1992, only 6–12% of patients classified as ADHD (by rating and/or by interview) were receiving stimulant treatment (Szatmari et al. 1989; Jensen et al. 1999b).

The prevalence of stimulant treatment by youths identified as having ADHD varies a great deal in relation to diagnostic precision, gender, age, year of treatment, severity, and other factors (Safer 2000). Considering that an estimated 3.5% of all public school students (K–12) in Maryland were receiving stimulant treatment in April 1998 (Safer and Malever 2000) and that 6–7% of children have substantive evidence for ADHD (Committee on Quality Improvement 2000), it is likely that approximately 55% of all U.S. youths diagnosed with ADHD were receiving stimulant treatment by the end of the 1990s. A recent small study of public school students (mean age 12 years) diagnosed with ADHD supports this estimate (Kaplan et al. 2000).

Lifetime Prevalence

Lifetime prevalence estimates of stimulant treatment for youths with a diagnosis of ADHD have frequently been based on data from clinic populations and therefore do not reflect the community rate (since many youths with ADHD features do not seek treatment). In clinic treatment studies, 52–71% of youths with a diagnosis of ADHD received stimulant treatment at some time before reaching adulthood (Bosco and Robin 1980; Copeland et al. 1987; Cullinan et al. 1987; Barkley et al. 1991).

In a 1992–96 community study, Angold and colleagues reported a 72% (81% male and 41% female) lifetime stimulant treatment rate for youths (ages 9–16 years) given a diagnosis of ADHD by a physician (Angold et al. 2000). In two studies of public school students performed in the 1970s requiring teacher, parent, and physician agreement for the diagnosis of ADHD, the lifetime prevalence of stimulant medication for students diagnosed with ADHD was 73% (Bosco and Robin 1980) and 86% (Lambert et al. 1981). When based on the findings from only one observer, the diagnosis and treatment rates were of course distinctly lower.

Differences exist between medication prevalence derived from large, computerized data sets and prevalence derived from epidemiological structured interviews of youths, e.g., the studies of Angold and Jensen discussed above. Results can be confusing to clinical readers because different conclusions should be drawn from each. In the epidemiological study, counting reassessed youths as ADHD-positive based on lay-administered checklist symptom criteria suggests that many youths go undiagnosed and further suggests that only a small proportion of these “true ADHD” youths actually receive medication. However, from community clinical data, the reader observes a widespread increase in stimulant use, presumably associated with the community-based physician diagnosis of ADHD or disruptive disorder. These findings may not be as contradictory as they appear on first inspection; the epidemiological data are based on a laboratory-based operational definition of ADHD, while the community data are based on the physician’s decision to initiate stimulant treatment. Neither finding addresses appropriateness directly. Such inferences from group data require details concerning severity of illness, patterns of therapy in the community, and short- and long-term treatment outcomes.

ADHD Treatment and Medication Visit Rates

A national survey of physician office visits, the National Ambulatory Medical Care Survey (NAMCS), offers an alternative to Medicaid or HMO health insurance claims data as a means of measuring the extent of medication utilization. Data from a survey of youths aged 5–14 years old who made medical visits to office-based physicians in 1996 showed that an estimated 3.6% were related to ADHD. Further, among ADHD visits, there was an increase in stimulant medication “mentions” from 62.6% to 76.6% across the 8-year interval (1989–96) (Zito et al. 1999b). Although treatment visit data cannot be directly compared with epidemiological data, the differences between them reveal quite a large variation in the proportion of ADHD-treated youths who receive medication. Consider the range that goes from a low estimate of 12% (8 of 66) of youths diagnosed with ADHD receiving stimulant treatment—based on a small sample from 1992 MECA data of Jensen et al. (1999b)—to a high estimate of 77% of ADHD visits to physicians—based on stimulant treatment from 1996 NAMCS data (Zito et al. 1999b). Clearly, broader and more detailed studies are needed.

Prevalence of Stimulant Medication Treatment for Youths

Point Prevalence Studies

In studies of public school students in Baltimore County, Maryland, the prevalence of stimulant medication treatment increased more than sixfold from 1971 to 1997 (Safer and Zito 2000). In April 1997 4.8% of all public school students

in that county were administered medication for ADHD (98% stimulants). In a 1996 survey of all public and parochial school students in a central Wisconsin school district, Musser and colleagues reported that 3.7% of the youths were administered stimulant medication (Musser et al. 1998). In two eastern Virginia public school districts in 1995–96, LeFever and colleagues in a 2nd through 5th grade survey reported that 12% of white and 6% of black students received stimulant medication for ADHD during school hours (LeFever et al. 1999). In a 1998 statewide survey of all public school students in Maryland (K–12), Safer and Malever presented findings that identified 2.81% of youths to be receiving stimulant medication during school hours (Safer and Malever 2000). In another 1998 study, a Rand report found that 3% of privately insured U.S. youths aged 6–17 years were being treated with stimulant medication (Stein et al. 2001).

Period Prevalence Studies

Rappley and colleagues, using 1992 triplicate prescription data from Michigan, found that 1.1% of youths under age 20 had been prescribed methylphenidate during a 2-month period (Rappley et al. 1995). Zito and colleagues, using 1994 Medicaid data from a mid-Atlantic state, reported a 4.6% one year prevalence of methylphenidate treatment for youths aged 5–14 years (Safer et al. 1996). Subsequent studies covering Medicaid enrolled youths in a midwestern state in 1995 found a one-year prevalence of 3.5% for youths under age 20 (Zito et al. 1998a) and a 1.2% one-year stimulant prevalence rate for youths 2–4 years of age (Zito et al. 2000b). In a similar analysis in 1998, Rushton and Whitmire reported a one-year stimulant treatment prevalence of 10.7% for North Carolina Medicaid enrolled youths 6–14 years of age (Rushton and Whitmire, 2001). Obviously, one should adjust for age and year to make fair comparisons of prevalence. Also, period prevalence rates covering an entire year are higher than those measuring medication use at one point in time (Khandker and Simoni-Wastila 1998). Consequently, comparisons between studies are difficult, and their differences are often substantial. Adoption of uniform standards for reporting prevalence would be a valuable tool for assessing population-based psychotropic practice patterns. As yet, such standards are not required or provided either by government, insurance, or provider organizations.

Patient Demographic Factors

Age-Specific Prevalence of Stimulant Medication for ADHD

Among youths with Medicaid insurance, peak stimulant medication usage occurred from 8 to 12 years of age (Zito et al. 1997). This is consistent with other surveys (Safer and Krager 1992; Rappley et al. 1995). In the large-scale 1992 study by Rappley and colleagues, the prevalence of stimulant treatment at age 10 was approximately double the rate at ages 6 and 14 (Rappley et al. 1995).

Gender-Specific Prevalence of Drug Therapy for ADHD

In Baltimore County public schools in the early 1980s, the male to female (M:F) gender ratio for youths receiving medication for ADHD was 6:1 in the elementary schools and 12:1 in middle schools. Since then, the gender ratio has steadily narrowed. In the 1990s, the M:F medication ratio dropped to 4:1 in the elementary schools and to 5:1 in the secondary schools (Safer et al. 1996).

The increased proportion of girls receiving medication for ADHD is now more in line with surveys of ADHD features from school samples, which consistently report a M:F ratio of 2:1 and 3:1 (McGee et al. 1987). The recent categorization of a predominantly inattentive subtype of ADHD within DSM-IV has increased the proportion of treatment-eligible girls above that of the earlier versions of the DSM (Gaub and Carlson 1997). It is probable that this development contributed to the narrowing of the M:F treatment ratio.

Race/Ethnicity-Specific Stimulant Prevalence

Maryland Medicaid prevalence for youths receiving stimulant medications has been tabulated by race/ethnicity. Such data from 1991 revealed that African American youths have a methylphenidate treatment prevalence 2.5-fold lower than their Caucasian counterparts (Zito et al. 1997). A similar twofold racial/ethnic disparity has been found by other investigators (Gadow and Kalachnik 1981; Cullinan et al. 1987; LeFever et al. 1999). In a 1998 Maryland statewide school-based survey, Safer and Malever reported that African American, Hispanic, Asian, and Native American students all had ADHD medication prevalence rates twofold or more below those of Caucasian students (Safer and Malever 2000). Of particular note is that the stimulant medication disparity of African American compared to Caucasian students in Maryland public schools increased in the higher grade levels and was highest in high school, when it rose to a five-fold difference (Safer and Malever 2000).

Prevalence Variation by Economic Status

Some reports indicate that youths in the lower socioeconomic class are less likely than their more affluent counterparts to receive stimulant medication for ADHD (LeFever et al. 1999; Ross 1979), whereas other reports have found no relationship between the use of stimulant medication and family income (Hansen and Keogh 1971; Bosco and Robin 1980; Safer and Krager 1992). In the Maryland public school survey of medication treatment for ADHD, there was no statistically significant rank order correlation between a county's median household income and the prevalence of school-administered medication for ADHD to students in that jurisdiction (Safer and Malever 2000). In that respect, the effect of income was clearly overshadowed by the significant effect of race. Weineck and colleagues reported similar findings using 1977–1996 data (Weineck et al. 2000).

Prevalence Variation by Geographic Region

In Michigan in 1992, prescription rates for methylphenidate varied 10-fold from county to county (Rappley et al. 1995). In Maryland in 1991 and 1998, such county and regional rates varied fivefold (Zito et al. 1997; Safer and Malever 2000). Some urban-rural differences have been reported in population-based studies (Conway 1976; Szatmari et al. 1989; Zito et al. 1997), but these differences appear to be relatively minor.

The Interaction of Race/Ethnicity, Economic Status, and Geographic Region

The Surgeon General's report on mental health (DHHS 2000) targets the need to resolve the large disparities in health outcomes based on racial/ethnic differences. Critical thinkers in health care warn researchers to avoid oversimplifying the explanatory role of race (Rivara and Finberg 2001). Thus, further study of the racial disparity regarding psychotropic medication should account for the interaction of race/ethnicity with economic status and geographic region. To be comprehensive, an explanatory model for psychotropic prescribing rates should also include parental education as a factor, as evidenced from a large survey finding from parents of youths receiving treatment for ADHD (dosReis et al. 1998).

Clinical Factors and Special Need Populations Influencing Drug Prevalence

Diagnostic Changes from DSM III to DSM IV

In 1980, an attention deficit came to be viewed by some influential researchers in the field as fundamental to the expression of overactivity in childhood (APA 1980; Carlson 1986). Consequently, hyperactivity was subsumed within attention deficit disorder (ADD). In 1987, the category name was changed to ADHD, and in 1994, additional changes occurred. In 1994, a subcategory "predominantly inattentive type" was specified, and hyperactivity was not required for a diagnosis of ADHD with this subtype.

Such diagnostic changes are still controversial (Barkley 1997), but the recent changes in the DSM had an impact on the prevalence of ADHD. In studies of the same youths diagnosed as ADHD using the DSM-III, -III-R, and -IV, researchers have consistently found more youths diagnosed with ADHD in association with each consecutive DSM-ADHD categorical change (Baumgaertel et al. 1995; Wolraich et al. 1996; Leung et al. 1996).

The bulk of the increase in the prevalence of ADHD since the diagnostic changes beginning in 1980 has been in youths with the inattentive subtype of ADHD. In the late 1990s, nearly half of the students rated by teachers as having the features of ADHD were in the predominantly inattentive subcategory (Baum-

gaertel et al. 1995; Wolraich et al. 1996; Gaub and Carlson 1997; McBurnett et al. 1998; Wolraich et al. 1998).

Empirical data on stimulant medication treatment rates for inattentive students show a similar rise. In the mid-1970s, Baltimore County clinic surveys indicated that only 7% of stimulant-treated youths were inattentive but not hyperactive. This proportional rate rose to 18% in the mid-1980s (Safer and Krager 1989). In a Tennessee Medicaid study in the early 1990s, it was 25% (Phillippi 1998).

Physician Specialty

Most prescriptions for stimulant treatment are written by pediatricians, followed by family practitioners and then by child psychiatrists (Gadow 1983; Wolraich et al. 1990; Rappley et al. 1995). Of note, Rappley and colleagues found in their 1992 study that 5% of pediatricians wrote 50% of the methylphenidate prescriptions written by that medical discipline (Rappley et al. 1995). A decade earlier, a similar unevenness in the pattern of prescribing by pediatricians was described (Bennett and Sherman 1983).

Medical Settings

In two studies covering the early 1990s, youths enrolled in a large HMO had a lower prevalence of stimulant treatment than did youths receiving Medicaid insurance (Zito et al. 1999a, 2000b). Likewise, in national surveys of U.S. outpatient physician visits covering 1985 and 1989–96, there was a lower prevalence of visits by youths for ADHD treatment in HMOs compared to visits reimbursed by Medicaid or by private fee-for-service payment arrangements (Kelleher et al. 1989; Zito et al. 1999b). One possible reason for youths with HMO coverage receiving relatively less medication for ADHD and fewer medication visits for ADHD is that more youths with Medicaid coverage are medically and chronically ill (Shatin et al. 1998; Kuhlthau et al. 1998). Geographic regional differences may also play a role in explaining variations between HMO and Medicaid rates.

Special Needs Groups: Youths with Mental Retardation and Foster Care Status

Mental Retardation

The prescribed use of stimulant treatment for ADHD in mentally retarded students in public schools ranges from 3.4% among the moderately retarded (Gadow 1985) to nearly 11% among the mildly retarded (Cullinan et al. 1987). Those most severely retarded seldom respond favorably to stimulant treatment (Gadow 1985), whereas mildly retarded youths with ADHD respond near the level of their nonretarded counterparts (Aman et al. 1991).

Foster Care Status

In a recent study of youths in foster care, 57% had developmental problems and over one third had mental health problems (Horwitz et al. 2000). In a 1996–1998 Los Angeles study of foster children aged 6–12 years of age, 9% of the boys were receiving prescribed stimulant medication during the month of the survey (Zima et al. 1999). In a 1996 Medicaid study in a mid-Atlantic state, dosReis and colleagues reported an 18% one-year stimulant medication prevalence for foster care youths under 20 years of age. This rate was 15-fold greater than that of Medicaid enrollees not in foster care and was distinctly higher than that of disabled youths receiving Supplemental Security Income (dosReis et al. 2001).

Medication Issues Related to Drug Utilization

Medication Regimen and Dosage Form

Whereas stimulant treatment was administered to youths primarily during the school year in the 1980s, this pattern changed beginning in the 1990s. Now a majority of youths are administered stimulant medication year-round (IMS Health 1998), the daily dose of stimulant medication has increased, and the short-acting tablets are administered commonly three times a day (MTA Cooperative Group 1999). One national physician audit estimated that the average dose of methylphenidate per patient year rose over 15% from 1990 to 1994 (Swanson et al. 1995b). These broadened medication administration patterns increase drug mentions, prescriptions, and bulk sales, although they obviously do not increase the number of individuals taking the medication.

The relative use of sustained-release stimulant tablets has not been systematically reported in the medical literature. However, with the marketing of a 12-hour duration, slow-release, three-compartment, plastic methylphenidate tablet in 2000 and with other promising new developments to provide long-acting stimulant formulations, community patterns of stimulant treatment administration could markedly change. As a result, the lunchtime dosing of school children for the treatment of ADHD will diminish.

Patient Adherence and Satisfaction with Treatment

Research indicates that patients' adherence to prescribed medications is less than complete. Generally, adherence rates for youths receiving methylphenidate range from 61% to 75% (Brown et al. 1987; Johnston and Fine 1993; Stine 1994). Nonadherence increases over time as treatment proceeds (Firestone 1982; Safer and Krager 1989) and becomes most prominent during adolescence (Brown et al. 1987; Safer and Krager 1989; Barkley et al. 1990). Given that treatment duration is being extended, adherence patterns should concern the clinical practitioner.

Adherence is improved by regularly reviewing teacher ratings and by monitoring dosing, side effects, and satisfaction with treatment (Weithorn and Ross 1975).

Prevalence of Stimulant Treatment According to Educational Setting and Category

Parochial and Private Schools

School surveys in Baltimore County, Maryland separately recorded the prevalence of stimulant medication treatment in parochial and private schools from 1971 to 1991. During that entire period the stimulant medication rate treatment in these schools rose along with the rate in the public schools, but continued to average only one-third that of treatment in public schools (Safer and Krager 1992). This appears largely accounted for by the fact that nearly one half of public school students medicated during school hours for ADHD receive special education services (Safer and Malever 2000). Such costly programs are uncommon in private and parochial schools. Selection bias may also contribute to these medication rate differences.

Public Schools

In the biennial surveys of medication treatment of Baltimore County students from 1971 through 1997, the prevalence of medication for ADHD rose more than 5-fold for elementary school students over that 27-year period, 10-fold for middle school students over a 22-year period (1975–1997), and 8-fold for high school students over a 15-year period (1983–1997) (Safer and Zito 2000). By 1997, the prevalence for ADHD for elementary school students (5.76%) was virtually the same as for middle school students (5.64%) (Safer and Zito 2000). Because 97% of all students receiving stimulants were first prescribed that treatment before or during their elementary school years (Safer and Krager 1994), the prominent secondary school stimulant medication prevalence increases since the 1980s have been largely due to the extended duration of that therapy.

Special Education

In Maryland public schools, students receiving special education services were administered medication during school hours for ADHD (96% stimulants) at a rate nearly 6 times greater than that of regular education students (Safer and Malever 2000). Viewed from another perspective, special education public school students represented 13.1% of the Maryland public school body in 1998, yet they received over 45% of the stimulant treatment administered during school hours (Safer and Malever 2000). The medication rate for students with ADHD in self-contained special education classes, a restrictive setting for the more serious cases, has ranged from 20% to 30% (Safer and Krager 1988; Bussing et al. 1998). The higher rate for these special education students is generally understandable

because approximately 33–42% of school-identified youth in special education classes have been diagnosed with ADHD (Charles and Schain 1981; Barkley et al. 1990).

Section 504 of the Rehabilitation Act of 1973

Students receiving Section 504 services are identified by schools on the basis of having an impairment that substantially limits their major life activities (Reid and Katsiyannis 1995). In the Maryland public school survey of 1998, 8.3% of all students administered methylphenidate during school hours were in this category (Safer and Malever 2000).

Other Factors Influencing the Prevalence of Treatment for ADHD

Pharmaceutical Promotion, Consumer Advocacy Groups, and Academic Thought Leader

The aggressive advertising campaign to market a mixed compound comprised of four amphetamine salts (dextroamphetamine sulfate and saccharate and amphetamine sulfate and aspartate), Adderal[®], for ADHD has sizably increased that drug's market share—even though in two recent small studies, dextroamphetamine sulfate had at least equal efficacy and a slightly longer duration than the four amphetamine salt compound (James et al. 2000; Gault et al. 1999).

Several advocacy groups for youths and adults with attention problems have emerged over the past decades. CHADD (Children and Adults with Attention Disorders) is the largest, with a membership of 38,000 across the United States. They provide useful local services in terms of resources for behavioral management, educational materials, and legal rights. Their indirect support of stimulants for the treatment of ADHD may be influencing their membership in this direction (Glusker 1997). Recently, CHADD has come under fire for accepting financial support from a major pharmaceutical manufacturer of ADHD medications, Ciba-Geigy (now Novartis), the maker of Ritalin[®] (Glusker 1997).

Academic thought leaders, through lectures and their writing, have an effect on prescription practices that is rarely appreciated or noted. For example, publications alerting physicians about the rare lethality of desipramine treatment for children with ADHD (Riddle et al. 1991) probably reduced sales (Vitiello et al. 1994), although it took a few years to have this impact (Zito, unpublished 1990–1993 mid-Atlantic state Medicaid data).

Impact of the Media and Threatened Law Suits

A campaign against Ritalin treatment for youths in the United States was spearheaded by a wing of the Church of Scientology in the late 1980s. As part of that campaign, media reports critical of Ritalin treatment appeared and lawsuits were

threatened or initiated. In cities where lawsuits were initiated, the anti-Ritalin media campaign had the effect of substantially reducing the number of youths placed on stimulant treatment for ADHD (Safer and Krager 1992). An analysis of wholesale pharmaceutical data on methylphenidate sales revealed that simply initiating lawsuits resulted in a far more profound decrease in that drug's usage than did media coverage without legal actions (Safer 1994).

U.S. Government Regulation

Methylphenidate (Ritalin), dextroamphetamine sulfate (Dextrostat[®], Dexedrine[®]), and Adderal are Schedule II controlled drugs regulated by the Drug Enforcement Administration (DEA). The DEA sets aggregate production quotas and has made efforts to keep them low, which on one occasion resulted in an unsuccessful legal attempt (in 1986) to enforce this (U.S. DEA 1995). In the mid-1990s, the DEA released an internal memo suggesting that abuse of methylphenidate was widespread and dangerous (U.S. DEA 1995).

Access to medications for appropriate use should be balanced against the control of an abusable substance. Increased methylphenidate treatment of adolescents would be likely to increase the opportunity for abuse as suggested by the anecdotes reported in the popular press (Ruley 1996; Stepp 1996). School surveys reveal only modest increases in the mid-1990s, but an increased rate in the latter part of that decade. Between 1991 and 1995, 1% or less of high school seniors reported the nonmedical use of methylphenidate (Maurer 1996; Goldman et al. 1998). A 1996 anonymous survey of Maryland high school seniors revealed a 2% nonmedical use of methylphenidate during the previous month, and a 1999 survey in Massachusetts revealed a nearly 13% nonmedical use of methylphenidate by high school seniors at some time in the past (Wen 2000).

International Perspectives on ADHD and Stimulant Treatment

The prevalence of the teacher-rated features of ADHD is generally similar in at least seven countries of the world (Glow 1980; Taylor 1987; Luk and Leung 1989; Szatmari et al. 1989). However, the prescribed use of stimulant treatment is profoundly lower in countries other than the United States and Canada (Swanson 1997). In the 1990s, stimulant treatment prevalence profoundly increased in the United States, Canada, and Australia (Hollander et al. 1996; Swanson 1997), although the overall rate is substantially less elsewhere (Swanson 1997). Specifically, the rate of stimulant treatment is low in Europe. Nonetheless, the sales of methylphenidate increased ninefold in the Netherlands from 1987 to 1996 (Council of Europe 2000) and more than fivefold in Germany from 1993 through 1998 (Poethko-Muller and Huss 2000).

A factor that partially accounts for the far higher stimulant treatment rate in the United States is its reliance on the DSM classification. Most European

countries use the ICD-9 and ICD-10 classification, which compared to the DSM nomenclature has a far more restrictive category, hyperkinetic disorder (Swanson et al. 1998). In evaluations of the same patients using the 314 DSM/ICD diagnostic code, prevalence rates of this disorder using the DSM III, III-R, or IV have been consistently and substantially higher than those using the ICD 9 and 10 (Prendergast et al. 1988; Taylor et al. 1991; Anderson and Werry 1994). Another reason for the low rate of stimulant treatment in most countries of the world is their tight legal restrictions (Safer and Krager 1984; Simeon et al. 1995). But, perhaps, a more fundamental factor relates to cultural differences. In some countries, antidepressants, anticonvulsants, and neuroleptics predominate over stimulants (Simeon et al. 1995; Minde 1998). In other countries, phytopharmaceuticals and homeopathic medicines predominate (Elliger et al. 1990).

ANTIDEPRESSANTS

There are a sizable number of epidemiological studies of antidepressant (ATD) treatments for U.S. adults (Pincus et al. 1998; Olfson et al. 1998), but very few that pertain to children and adolescents. What is primarily available in the literature relating to ATD treatment of youths are medical chart reviews from clinic surveys, prescription data—mainly from marketing firms—and modest-sized surveys of physician visits, which include whether or not an ATD medication was prescribed. Although the published findings are few in respect to rates of ATD treatment in youths, all the available data point to a substantial and consistent increase in ATD treatment for children and adolescents during the 1990s (Strauch 1997).

Clinic Surveys of ATD Treatment of Youths

Medical chart analyses covering the years 1988–1992 and 1990 revealed that 24–31% of the children prescribed psychotropic medication in selected child mental health clinics in three states had been prescribed ATDs (Safer 1997; Kaplan et al. 1994). In a residential treatment setting in 1991–1993, 22% of the youths receiving psychotropic medication were prescribed ATDs (Connor et al. 1998). In three inpatient settings in 1991, 26–80% of the youths receiving psychotropic medication (representing 68–79% of the total number admitted) were given a prescription of ATDs upon discharge (Kaplan and Busner 1997). Last, in a review of summary reports from seven child/adolescent primarily general hospital inpatient units during the years 1988–1994, 43–53% of the youths were prescribed an ATD at or before discharge (Safer 1997). Clearly, ATDs were being prescribed to a very sizable proportion (approximately 25–50%) of youths receiving psychotropic treatment in the 1990s, particularly for inpatients.

Prescription Data on ATD Treatment of Adolescents

Prescription sales of ATDs, particularly for adolescents, rose substantially throughout the 1990s. From 1995 to 1996, prescription sales of selective serotonin reuptake inhibitor (SSRI) antidepressants for youths rose 59%, with adolescents aged 13–19 years experiencing the highest rate of increase (Strauch 1997). In a two-state 1990 Medicaid study assessing psychotropic prescription patterns for youths, 40–45% of the total prescriptions for youths aged 15–18 years were ATDs (Buck 1997).

Tricyclic Antidepressant Utilization for Enuresis

In addition to treating depression, ATDs have been used to treat childhood enuresis. In 1975, a large sample of the parents of children aged 5–13 years were asked about the management of their child's enuresis. Of the children treated by a physician for this condition, 48% received a medication for it, primarily a tricyclic antidepressant (TCA), imipramine (Foxman et al. 1986). In a physician survey—with a 62% response—published in 1984, 40–50% of the physician respondents indicated that TCAs were their first-line approach to treating enuresis (Raubert and Maroncelli 1984). Apparently, the treatment pattern has since changed a great deal, because in 1994 only 2% of Medicaid-enrolled youths aged 2–19 years receiving an ATD received prescribed TCAs to treat enuresis (Zito et al. 2001).

ATD Utilization Studies

In a 1995 survey based on a national probability sample of office-based, nonsalaried physicians, ATDs were the second most commonly prescribed psychotropic medication group after stimulants. Among ATDs, SSRIs were more commonly prescribed than TCAs (Jensen et al. 1999a).

ATD Prevalence Studies

Between 1988 and 1994, the one-year prevalence of ATDs for youths aged 2–19 years enrolled in two state Medicaid insurance programs and in one staff-model HMO rose 3- to 5-fold (Zito et al. 2000a, 2001). Over that period, the prevalence of TCAs rose 2- to 3-fold for these youths, but as a proportion of all ATDs, TCAs declined because the SSRIs and other ATDs rose over 19-fold. Similarly, Rushton and Whitmire, assessing North Carolina Medicaid ATD data for youths aged 6–14 years, reported a 17-fold prevalence rise for SSRIs from 0.1% in 1990 to 1.7% in 1998 (Rushton and Whitmire, 2001).

In 1996 the one-year prevalence of ATD treatment for youths less than 20 years of age was 2% in a midwestern Medicaid database, making these drugs the second most prescribed psychotropic medication group after stimulants (Zito

et al. 1999a). For the Medicaid enrollees prescribed an ATD in 1996, approximately one half were receiving TCAs. For the staff-model HMO enrollees (<20 years), only 36% of those prescribed an ATD received a TCA (Zito et al. 2001).

Gender-Specific ATD Medication Patterns

Over the period 1988–1996, there was a proportionately greater increase in ATD treatment in male than in female youths in the Medicaid databases from two states (Zito et al. 2000c). The overall M:F ratio widened during that period from 1.5:1 to 1.9:1 and from 1.0:1 to 1.3:1. In the HMO dataset, proportionally more boys were placed on antidepressants than girls in the 0–4, 5–9, and 10–14 year age groupings, but the reverse was the case for youths in the 15–19 year age group. Because of far larger late adolescent ATD usage, the overall M:F ratio for the HMO narrowed to 0.8:1 over the 9-year period (Zito et al. 2000c). By these measures, ATD use appears to be equalizing among late adolescents and to be male predominated among early adolescents.

Race/Ethnicity-Specific ATD Medication Patterns

In 1991, African American youths with Medicaid insurance aged 5–14 years were less than one half as likely to be prescribed ATD medication as their Caucasian counterparts (Zito et al. 1998b). This racial disparity for ATD treatment decreased somewhat between 1988 and 1996 (Zito et al. 2000c). The Caucasian/African American disparity in ATD treatment was greatest for the 15–19 year age group in the 1996 Medicaid datasets (Zito et al. 2000c).

The Caucasian/African American psychotropic medication disparity for youths as well as for adults has been corroborated by several other investigators. Khandker and Simoni-Wastila (1998) found the same disparity using 1992 Georgia Medicaid data. Melfi and colleagues (2000) using 1989–1994 Medicaid data from one state reported this phenomenon for all age groups. Furthermore, when combining Medicaid data from all age groups, they reported that Caucasians were more likely than African Americans to be prescribed SSRIs than TCAs (Melfi et al. 2000), a finding noted also by Zito and colleagues (2000c).

Diagnosis and Medical Specialty Associated with ATD Treatment for Youths

In 1994 Medicaid data, the most common psychiatric diagnoses associated with ATD treatment of youths by primary care providers were ADHD followed by depression. That diagnostic ranking was reversed for youths receiving ATDs from psychiatric service providers (Zito et al. 2001).

In 1994, SSRIs were the predominant treatment for Medicaid-enrolled youths with a sole diagnosis of depression, and TCAs were the predominant

ATD treatment for youths with a diagnosis of ADHD or conduct disorder. In one Medicaid dataset, 56% of youths aged 2–19 years prescribed ATDs were treated exclusively by their primary care provider (Zito et al. 2001).

Adult Versus Late Adolescent Patterns of ATD Treatment

Physician-based surveys of medical visits in 1985 and in 1993–94 (Pincus et al. 1998; Olfson et al. 1998) revealed that ATD treatment trends for U.S. adults were similar to those from 1988 through 1994 for late adolescents (aged 15–19) reported by Zito and coworkers (Zito et al. 2001). The adult/late adolescent similarities reported include a twofold or greater increase in ATD prevalence over the 7- to 8-year period, an SSRI proportion approximating 50% of ATD usage in 1994, a preponderance of females among those treated with ATDs, ATD treatment associated primarily with a diagnosis of depression, and relatively more psychiatric service than primary care providers when ATD recipients received a diagnosis of depression along with other psychiatric diagnoses (Zito et al. 2001).

The adult/late adolescent similarities highlight the contrast between the ATD treatment patterns of late adolescents and those under age 15. For youths under age 15 in 1994, TCA usage was predominant, the recipients were primarily male, the primary diagnoses associated with ATD treatment were ADHD and disruptive behavior, and multiple psychiatric diagnoses were relatively uncommon (Zito et al. 2001).

α -AGONISTS

Two α -agonists, clonidine and guanfacine, have become increasingly prescribed for emotional and behavior disorders in youth. The proportion of guanfacine grew more rapidly than clonidine from 1990 to 1996 (Zito et al. 1999a). Nonetheless, in 1996, in two Medicaid and one HMO datasets, clonidine still represented 89–95% of the α -agonist total (Zito et al. 1999a).

In the 1980s, α -agonists were rarely prescribed for psychiatric purposes in children. From 1987 through 1990, the prevalence of α -agonists (specifically only clonidine) in the three large databases rose on average from 0.01% to 0.03% in youths under age 20 years. By 1996, the prevalence of α -agonists in the two Medicaid datasets rose to 0.73%, and the HMO prevalence of α -agonists rose to 0.39% (Zito et al. 1999a).

Swanson and colleagues cited a Scott-Levin Drug Audit indicating an 8-fold increase in clonidine prescriptions from 1990 to 1995 (Swanson et al. 1999). Based on the 1996 prevalence of alpha-agonists in one large HMO dataset (Zito et al. 1999a), it is estimated that 300,000 youths under age 20 received those drugs that year.

Age-, Gender-, and Race/Ethnicity-Specific Patterns of α -Agonists

α -agonist prevalence was highest in the 10–14 year age group in the two Medicaid sites in 1996 (1.3–1.5%). In the HMO site, the prevalence was highest in the 5- to 9-year-old age group (0.6%). The M:F gender ratio widened from an average of 2:1 to 4:1 in all three databases from 1987 through 1996. By 1996, the M:F ratio in all three sites ranged from 4:1 to 5:1. The Caucasian/African American ratio for α -agonists in youth ranged from 1.9:1 to 2.3:1 in the two Medicaid databases in 1996. It was most disparate in the 15–19 year age grouping in 1996 (2.3:1 and 3.1:1) (Zito et al. 1999a).

Diagnosis and Treatment Combinations Associated with Clonidine

Clonidine, when used for psychiatric purposes in youth, is prescribed primarily for ADHD and behavior disorders (Connor et al. 1998; Wilens and Spencer 1999). It is often used in combination with stimulant medication. In ADHD youths it is frequently used to treat insomnia (Prince et al. 1996).

NEUROLEPTICS

Clinical surveys suggest that neuroleptic (antipsychotic) medication has been primarily prescribed to U.S. youths for the treatment of aggression (Kaplan et al. 1994; Kaplan and Busner 1997; Connor et al. 1997). In outpatient child mental health clinics in three states in 1990, chart reviews revealed that neuroleptic use ranged from 4% to 37% (Safer 1997). Obviously, the frequency of outpatient neuroleptic treatment for youths varies a great deal by site, but its use is certainly higher for those psychiatrically hospitalized than for outpatients. Examples of the rate of inpatient neuroleptic treatment for youths are:

1. Zito and colleagues reported that 51% of 267 youths in four inpatient sites in New York State had been prescribed neuroleptics during a 3-month period in 1990 (Zito et al. 1994).
2. Kaplan and Busner reported neuroleptic treatment of adolescent inpatients in three different hospital settings that ranged from 35% to 74% during 1991 (Kaplan and Busner 1997).
3. Connor and colleagues found that 35% of youths (mean age 13.6 years) in a residential center were receiving neuroleptics in 1991–1993 (Connor et al. 1998).

Neuroleptic use is also greater in boys, youths with mental retardation, other developmental disorders, and in psychotic disorders (Aman et al. 1995; Galton

et al. 1998). Unlike provider patterns in stimulant treatment, neuroleptics are more commonly prescribed by psychiatrists than by primary care physicians (Zito et al. 2000a).

Utilization Rates of Neuroleptic Treatment

Based on 1991 Medicaid prevalence data from one state, neuroleptic medication treatment was the third most utilized psychotropic medication subclass after stimulants and antidepressants (Zito et al. 1998c). That rank order was also apparent in 1992 marketing data of youths less than age 19 (Jensen et al. 1994). However, by 1995 neuroleptic utilization dropped to fourth place, after α -agonists (Jensen et al. 1999a).

Between 1990 and 1996, the prevalence of neuroleptic treatment for youths less than 20 years of age rose 63% in one state Medicaid database. In 1996, 0.6% of Medicaid-enrolled youths in that state had received one or more prescriptions for a neuroleptic (Malone et al. 1999). By 1996, second-generation neuroleptics (e.g., risperidone) comprised 45% of the total prescribed (Malone et al. 1999). In the 1991 Medicaid data from one state, the Caucasian:African American ratio for neuroleptic treatment was 2.1:1 in youths aged 5–14 years (Zito et al. 1998b).

CONCOMITANT PSYCHOTROPIC MEDICATION TREATMENT OF YOUTHS

Concomitant psychotropic medication for youth substantially increased during the 1990s. From 1990 to 1994, the average rate of concomitant psychotropic medication treatment for youths in four outpatient mental health clinics rose 133% (Safer 1997). Between 1987 and 1995, Zito et al. reported a 2.4-fold proportional increase in Medicaid enrolled youths receiving three or more psychotropic medications (Zito et al. 1998a). In a national sample of physician visits, the rate of adding an antidepressant to a stimulant medication rose from 4% in 1994 to 29% in 1997 (Bhatara et al. 2000).

In mental health clinic reports from three states, the rate of concomitant psychotropic medication treatment in 1990 ranged from 9% to 18% (Kaplan et al. 1994; Safer 1997). In 1997, a report from one Maryland clinic revealed this rate to be 22% (Storch 1998). In December 1996, a physician practice network survey revealed that 49% of 166 youths treated for ADHD were concomitantly receiving more than one psychotropic medication (Zarin et al. 1998).

Particularly common outpatient combinations are methylphenidate and clonidine and stimulants and antidepressants. In the early 1990s, Swanson and colleagues reported that 41% of youths receiving clonidine also received methylphenidate (Swanson et al. 1995a), whereas Prince et al. reported this figure to be 68% (Prince et al. 1996). Pathiyal et al. reported that 22% of those receiving

methylphenidate in 1993–95 were also receiving antidepressants (Pathiyal et al. 1998), and Zito et al. found that one third of Medicaid-enrolled youths receiving antidepressants in 1994 had also been prescribed a stimulant during that year (Zito et al. 2001). Rushton and Whitmire reported that 30% of those receiving an SSRI in 1998 also received a stimulant that year (Rushton and Whitmire 2001). In a residential treatment setting, the combination of a neuroleptic and lithium comprised 25% of the “polypharmacy” in 1991–1993 (Connor et al. 1998).

The rates of concomitant psychotropic treatment for youths with a developmental disorder, a serious emotional disorder, or a foster care placement have generally been higher than the average for less impaired youths seen in public mental health clinics. Multiple medication treatment for youths in special education classes because of serious emotional disorders was 17% in 1993–94 (Mattison 1999). For youths with pervasive developmental disability, the concomitant use of psychotropic medications in 1997 in one university outpatient clinic was 29% (Martin et al. 1999). In the early 1990s, the parents of autistic youths who were surveyed by mail reported that 28% of these youths who were medicated were receiving multiple psychotropic agents (Aman et al. 1995). In 1996–98, a foster care assessment of 302 children revealed that 18% of the youths medicated with psychotropics were taking a combination of agents (Zima et al. 1999).

Concomitant use of psychotropics has become particularly common for youths in inpatient psychiatric units and in residential treatment centers. In a 1991 medical chart audit, Kaplan and Busner found that 48% (51/107) of medicated New York State adolescent inpatients were receiving more than one psychotropic agent concomitantly (Kaplan and Busner 1997). Using 1994 data from seven Maryland inpatient units, Safer found that the concomitant psychotropic treatment rate (excluding anticholinergics) for all inpatient youths was 42% (28/66) (Safer 1997). Reporting on the rates in residential treatment centers for 1991–93, Connor and colleagues found that 57–60% of youths referred for admission had a history of combined pharmacotherapy, and that 39.7% (33/83) of those when seen on admission were receiving more than one psychotropic agent (Connor et al. 1997, 1998).

The concomitant use of psychotropic medication in youths has received virtually no research assessment (Vitiello and Hoagwood 1997). Numerous case reports indicate that concomitantly using three or more psychotropics in prepubertal youths can be particularly hazardous (Budman et al. 1995; Preda et al. 1998; Sallee et al. 2000), and in empirical studies of adults, adverse drug reactions have been shown to increase in proportion to the addition of other medications (Colley and Lucas 1993; May et al. 1977). Consequently, in June 2000 the Council of the American Academy of Child and Adolescent Psychiatry adopted a policy statement urging caution in the prescribing of multiple psychotropic medications for the pediatric population (AACAP Council 2000).

SUMMARY

Overall, psychotropic medication prevalence increased two- to threefold from 1987–1996 in youths < age 20 in the U.S. based on computerized data from three large sites. The major trends in psychotropic medication over that decade for youths are as follows:

- Stimulant treatment rose proportionately more for females and for youths in the preschool (2–4) and late adolescent age groups (15–19 years).
- Antidepressant treatment rose proportionately more in males and for youths in the preschool (2–4) and late adolescent age groups (15–19 years).
- α -agonist treatment rose proportionately more in males and for youths 5–14 years old.
- Total neuroleptic medication prevalence rose moderately in the first half of the 1990s, but the use of second-generation compounds had a prominent increase then.
- Concomitant psychotropic medication treatment rose two- to threefold for youths.
- Although racial disparities had some narrowing of the gap, more empirical attention is needed to address the relative acceptability of psychotropic medications across race/ethnicity groups.

Numerous questions can be raised by the pharmacoepidemiological findings reported herein. These include clarifying the following: (1) TCA treatment of depressed youths, (2) concomitant use of SSRIs and stimulant medication, (3) concomitant use of an α -agonist and a stimulant, (4) neuroleptic treatment for disruptive disorders in youths, (5) continuing sizable racial/ethnic disparity in psychotropic treatment, (6) geographic differences in medication treatment patterns, (7) increasing preschool usage of psychotropic medication, (8) primary care providers as major prescribers of selected psychotropic medication for youths, (9) the medical and social impact of continuing increases in psychotropic medication for youths, and (10) how appropriateness of psychotropic prevalence can be subjected to rigorous assessment using community-based treatment outcomes rather than being merely debated.

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Child and Adolescent Psychopharmacology: A Call for Pharmacoeconomics Research

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INTRODUCTION

Over the past decade, health care policymakers and clinicians have been contending with the impact of neuropsychiatric disorders on the morbidity, mortality, and quality of life of patients and their families. In addition to ever-increasing data about the costs of neuropsychiatric disorders, newer data about the profound disablement incurred by these disorders have resulted in increased national and international attention. In the United States, mental disorders collectively account for more than 15% of the overall burden of disease from all causes and slightly more than the burden associated with all forms of cancer (Lopez et al. 1998).

The views expressed in this paper are the authors' and do not necessarily represent those of the National Institute of Mental Health.

Several exciting national directives and projects emerged from the highest levels of U.S. health care policy: a 1999 White House Conference on Mental Health, the 1999 Surgeon General's Call to Action to Prevent Suicide, the first ever Surgeon General's 1999 Report on Mental Health, and a 2000 Surgeon General's Conference on Children's Mental Health.

These efforts were underscored by reported productivity losses and high indirect costs of neuropsychiatric disorders to society. Data developed by the massive global Burden of Disease Study (Lopez et al. 1998) revealed that mental illness, including suicide, ranks second in the burden of disease in established market economies such as the United States. Depression, for example, was the fourth leading cause of disease burden in 1990 and is expected by 2020 to be the single leading cause.

Many neuropsychiatric disorders begin in childhood and adolescence, and many children have mental health problems that impair their normal development and functioning (Roberts et al. 1998). U.S. data indicate that nearly 10% of children and adolescents suffer from psychiatric disorders severe enough to cause some level of impairment (Costello et al. 1996; Leaf et al. 1996). Estimates also indicate that the unmet need for services for these children is the same as, if not greater than, 20 years ago. Data from the World Health Organization (WHO) indicate that by 2020, childhood neuropsychiatric disorders will rise by over 50% worldwide and push these disorders into being one of the top five causes of disease burden in children.

The MECA (Methodology for Epidemiology of Mental Disorders in Children and Adolescents) study estimated that nearly 21% percent of children aged 9–17 years in the United States had a diagnosable mental disorder associated with at least some degree of impairment (Leaf et al. 1996). Even when using diagnostic criteria requiring significant functional impairment, 11% of children are affected—an estimate that translates into 4 million U.S. youth who suffer from a mental disorder and have impaired school, family, and interpersonal functioning.

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed mental disorder in childhood, occurs in nearly 5% of school-age children, and is more common in boys than girls (Shaffer et al. 1996; MTA 2000). Children with ADHD can experience long-term effects on academic performance, vocational success, and interpersonal development. Finally, some children have ADHD that persists into adulthood. A new study highlighted the costs of ADHD (Leibson et al. 2001), but resources spent go beyond the health care system. Social, educational, and other service sectors serve these children and their families but are often fragmented and not tallied in accounting costs (Chatterji et al. 2000; Rones et al. 2000)

Depression in children and adolescents has many features similar to that in adults, and an episode can last from 7 to 9 months (Birhamer et al. 1996).

One characteristic of the disorder is that when depressed, children tend to be self-critical and feel others are critical of them as well (Hammen et al. 1996). Some studies estimate the prevalence of childhood and adolescent depression as 2.5% and 8.3%, respectively (Shaffer et al. 1996) and the prevalence of depressive symptoms in adolescence not meeting criteria for major depression to be between 10 and 15%. Twenty to 50% of depressed children and adolescents have a family history of depression (Lewinsohn et al. 1994). Depressive disorders place both children and adolescents, at risk for impaired interpersonal, psychosocial, and vocational functioning that persists after resolution of the depressive episode. In adolescents, depression also confers increased risk for substance abuse and suicidal behavior. Early diagnosis and treatment of depressive disorders are critical for healthy emotional, social, and behavioral development.

Over the last 15 years, as escalating health care expenditures spiraled upward, the term “cost-effective” has been commonly used in clinical practice, tossed about by policymakers, industry, managed care organizations, and the media, and often not used in an appropriately precise manner. The state of the science was considered to reflect some of this imprecision and variability. In point of fact, much of this variability stemmed from the different needs of the purveyors of the phrase—disease advocacy groups and purchasers of insurance plans would certainly want and need to use a term like cost-effective in different ways and for different purposes.

In 1993 the U.S. Public Health Service (PHS) created and charged a group of 13 experts in cost-effectiveness analysis (CEA) to provide guidelines for the conduct of such studies in order to improve these types of studies and allow comparability between them. This Panel on Cost-Effectiveness in Health and Medicine published its findings in a 1996 book (Gold et al. 1996), which delineated state-of-the-art methodologies for the different elements in a CEA and, perhaps more importantly, set forth recommended elements that should be overtly included in technical and journal reports. For example, the book highly recommends the use of a reference case in presenting a CEA—this reference case is

a standard set of methodologic practices that an analyst would seek to follow in a cost-effectiveness study . . . [it] would serve as a point of comparison between studies . . . although an investigator might well choose to include other cases in a study with assumptions and methods that differ from those in the Reference Case. The results for the Reference Case in any two studies could then be compared with confidence that the comparison is an appropriate one. The larger the number of CEAs that include a Reference Case, the larger the number of meaningful comparisons. Thus each study contributes to a pool of information about the broad allocation of resources as well as to the specific questions it was designed to answer.

In addition to the recent deserved attention to the high and early burden of neuropsychiatric disorders in children and adolescents and the issue of rising health care costs and rapid evolution of managed care is the observation that now the largest portion of health care cost rise is pharmaceuticals and that a major subgroup of this pharmaceutical cost rise is psychotropics (Cooke 1994, Foote et al. 2000). Furthermore, this expenditure rise has been linked to a national rise in health care insurance premiums. Never has the study of pharmacoeconomics been needed more— an area of study defined as “that which describes, measures, analyzes, and compares the costs, or resources consumed and outcomes including consequences of pharmaceutical products” (Detsky 1994; Schulman 1996).

This chapter summarizes critical elements of and developments in pharmacoeconomics, presents the major types of cost analyses and their important variable domains, highlights the complexities in issues such as data sources (Clemens et al. 1995), describes recent conceptual and practical concerns in using cost analyses, and concludes with summarizing “real world” difficulties in applying cost studies to real decision making (Chisholm 2000). Despite the existence of clinical trials of medications for ADHD and childhood depression over the last decade (Puig-Antich et al. 1987; Geller et al. 1989; Emslie et al. 1997; MTA 1999), no published cost studies of psychotropics for children or adolescents exist. Currently, studies of psychotropic medication for children are underway that will include some cost assessments.

PHARMACOECONOMIC ANALYSES

Introduction

As noted earlier, the rise in health care expenditures, especially pharmaceutical products, led to major changes in health care delivery via managed care in the United States., as well as the adoption of guidelines for pharmacoeconomic analyses by national purchasers such as the Australian government. At first glance, the uses of pharmacoeconomic analyses would be appealing to several decision makers: providers, large purchasers (such as employers and payers), and policymakers. For provider groups, formulary decisions, guidelines development, and disease management strategies could springboard from cost analyses (Davey et al. 1994). For large purchasers, coverage decisions and even choice of performance measures (e.g., quality) might be affected (Cooke 1994). Finally for policymakers, cost analyses may abet resource allocation decision and the valuation of new technologies. However, we are a long way from implementing these applications into real-time decisions given recent concerns, which range from conceptual to methodological to practical (Drummond 1994).

The field of health economic evaluations has seen a dramatic growth in the past decade. Anell and Norinder’s recent review analyzed 455 studies from 1986

to 1997 and found that the number of such studies increased 10-fold since 1990 (Anell et al. 2000). Of the three types of cost analyses, 80% were cost-effectiveness studies, 17% cost-utility studies, and 3% cost-benefit reports. From 1986 to 1996, Anell found 21 cost studies on mental disorders, and 4 others were labeled “nervous system.”

As noted earlier, some national applications of cost studies to inform policy are in place (Jacobs et al. 1995). For example, the Australian Pharmaceutical Benefits Scheme’s recent report reviewing pharmacoeconomic analyses submitted for possible listing of a pharmaceutical product on the government’s formulary underscores the complexity of such endeavors (Hill et al. 2000). This Pharmaceutical Benefits Scheme is a comprehensive and national insurance program that covers prescription drugs using copayments and rankings of drugs according to their comparative effectiveness and cost-effectiveness. Of 326 submissions between 1994 and 1997, 218 had significant problems in four general categories: estimate of comparative clinical efficacy, comparator issues, modeling problems, and calculation errors. Ten types of errors emerged within these categories ranging from poor quality of the trials, use of inappropriate comparators, problematic assumptions in the model, and uncertainties about costs. Despite the so-called availability of studies, the Australian experience identifies clear gaps in need of attention.

Another critical issue has been the source and funding behind pharmacoeconomic studies. For nearly 15 years concerns were raised about the conduct of industry-sponsored pharmacoeconomic studies since the potential biases were both quantitatively and qualitatively serious. In 1995, the Pharmaceutical Research and Manufacturers of America (PhRMA)—the major trade association for the pharmaceutical industry—developed and recommended, for voluntary use, principles for pharmacoeconomics covering both methodology and reporting. (Clemens et al. 1995) Furthermore, practical and ethical issues arise when industry sponsors outside researchers to conduct pharmacoeconomic evaluations (Schulman 1993; Schulman et al. 1995)

This complex issue was the topic of a recent editorial by Rennie and Luft, who wrote: “Is it possible to publish credible cost-effectiveness analyses sponsored by drug companies? We’ll see, but we will see only if we can see all the data” (Rennie and Luft 2000). One review found that industry sponsored pharmacoeconomics studies were only one-eighth as likely to have negative conclusions and 1.4 times as likely to have favorable conclusions as studies not funded by pharmaceutical companies (Friedberg et al. 1999). PhRMA’s rebuttal to this was that there was already selection bias since analyses were done on drugs that were highly effective anyway. But as Rennie and Luft wrote, “this does not explain why a higher proportion of nonprofit-sponsored cost-effectiveness analyses of drugs already on the market are negative and why the evidence from other studies . . . confirms that the process is skewed.”

It is clear that the quality of cost analyses is only as good as the trials on which they are based. O'Brien (1996) noted that traditional clinical trials measure efficacy of an agent and that the use of these results in cost-effectiveness analyses presumes effectiveness in broader populations—a presumption that is misguided due to the nature and intent of the original trial. He notes several other difficulties: lack of relevance of placebo trials (i.e., no head-to-head comparator); relevance of the short-term often surrogate outcomes in the trial; small sample sizes; inadequate follow-up; and lack of generalizable results. He sums up the potential difficulties by writing, "Simply tacking on an economic analysis to a premarketing RCT may be inadequate for competent economic studies."

Types of Pharmacoeconomic Studies

The economic concept of efficiency girds pharmacoeconomics studies: Are resources (often limited) being optimally utilized to obtain the best outcome? In the case of drugs, is the cost of a pharmaceutical drug really worth the therapeutic benefit of that drug? The three most commonly used economic analysis types are cost-minimization, cost-benefit, and cost-effectiveness. Table 1 contains definitions of common terms and cost concepts.

Cost-minimization studies are also known as cost-identification or cost-efficiency analyses and are used when there is evidence that interventions are equally effective. Cost-minimization analysis is the least complex of economic studies and identifies the costs involved in either determining the least costly diagnostic or therapeutic approach. Since the compared interventions or approaches are equivalent in their effectiveness, there is no need to consider outcomes (Glick et al. 1992; Eisenberg et al. 1994). This is, however, its limitation. These studies are used when decision makers are choosing the least costly alternative for the same desired outcome. One advantage of cost-minimization studies is the need to collect only cost data, not outcome data.

Cost-benefit analysis (CBA) is performed when both costs and outcomes are measured, expected to vary, and when outcomes can be expressed in monetary units such as dollars. Disparate programs or interventions can be compared when this type of analysis between costs and outcomes can be realized at a dollar level. CBA uses two main measures: the ratio of dollars spent to dollars saved and the net saving or cost. While CBA is appealing theoretically, in practice CBA may fall short of assigning valid dollar values to all outcomes. Health programs or interventions may be more susceptible to interpretation problems if using CBA because the outcomes may be varied and multidimensional (e.g., change in mood symptoms, medication side effects, and social functioning). For example, assessing a medication's impact on additional years of life is not easy when the illness may not be acutely life threatening.

Cost-effectiveness analysis (CEA), like cost-benefit analysis, is used when both costs and outcomes are expected to differ, and it has been utilized more because it allows the incorporation of multidimensional outcomes beyond clinical symptomatology (Coast 1993). CEA allows costs to be expressed in units such as dollars, yet outcomes can be expressed in numerous ways, such as averted complications or years of life saved or gained: CEA allows outcomes to be combined on a common scale. Since decision makers are often faced with the difficult task of trying to integrate different outcomes to assess overall effectiveness, the CEA allows the combination of several outcomes into a common unit or scale such as a quality-adjusted life-year (QALY), which uses both the duration and quality of life during survival. Recent work has recommended alternatives to the QALY and noted major conceptual difficulties. (Gafni et al. 1993; Ubel et al. 2000; Matcher 2000).

Two main approaches to CEA exist: the first determines separate CE ratios as costs divided by outcomes when separate interventions are compared, and the second compares incremental costs and incremental benefits. Treatments that show cost savings or equivalence with better or equal outcomes are said to be dominant and should be selected (Schulman 1996).

Cost-utility analysis (CUA) is an enhanced form of CEA that allows the relative importance of multiple outcome domains to be valued. CUA uses a utility measurement approach to determine quantitative values, or utilities, to different outcomes. These approaches can yield numeric weights that can be combined with the outcomes of interest to get a single core for a combination of seemingly disparate outcomes. Using utility-based outcomes is important, especially when there may be trade-offs between outcomes (e.g., intolerable or dangerous side effects from a medication with good therapeutic effect). The utilities generated use a metric where 1 represents perfect health and 0 represents death. These are easily combined into a unit such as QALY. However, the conceptual and measurement issues are exceedingly complex for utility assessment (Froberg et al. 1989 a–d).

Finally, CEA come in two forms: marginal and incremental cost-effectiveness. According to Eisenberg, “marginal cost-effectiveness represents the additional cost and effectiveness that may be obtained from one additional unit of service. In contrast, incremental cost-effectiveness represents the additional cost and effectiveness obtained when one option is compared with the next most intensive or next most expensive alternative” (Eisenberg et al. 1994).

The popularity of CEA is understandable, since it allows the decision maker to consider exchanging better outcomes for more money and avoids the translation of clinical or quality of life outcomes into dollars. In the calculation of cost-effectiveness ratios (not discussed here), there is no ideal or standard ratio for which to aim.

TABLE 1 Glossary of Terms Used in Health Economic, Pharmacoeconomic, and Quality of Life Analyses

Term	Definition/Description
Acquisition cost	Purchase cost of a drug to an institution, agency, or person
Analytic perspective	Viewpoint chosen for the analysis (e.g., societal, government, health care system, payer)
Average cost	Total costs of a treatment or program divided by total quantity of treatment units provided (see also Marginal costs)
Contingent valuation	Method for evaluation of benefit or value to individuals of therapy that uses survey methods to establish willingness to pay.
Cost/QALY gained	Measure used in cost-utility analysis to assist in comparisons among programs; expressed as monetary cost per unit of outcome
Cost-benefit analysis (CBA)	Type of analysis that measures costs and benefits in pecuniary units and computes a net monetary gain or loss or a cost-benefit ratio
Cost-benefit ratio	Ratio of the total monetary cost of a program divided by the benefits expressed as savings in projected expenditure
Cost-effectiveness analysis (CEA)	Type of analysis that compares drugs or programs having a common health outcome (e.g., reduction of blood pressure, life-years saved)
Cost-effectiveness ratio	Ratio of the total cost of a program divided by the health outcome (e.g., cost per life-year gained); used in CEA to select program
Cost-minimization analysis	Type of analysis that finds the least costly program among those shown or assumed to be of equal benefit
Cost(burden)-of-illness	Study that identifies and evaluates the direct and sometimes indirect costs of a particular disease or risk factor (e.g., smoking or alcohol consumption)
Cost-utility analysis (CUA)	Type of analysis that measures benefits in utility units or quality-adjusted life-years (QALY); computes a cost per utility-measure ratio between programs
Decision analysis	Explicit quantitative approach for prescribing decisions under conditions of uncertainty
Decision tree	Framework for representing alternatives in use in decision analysis
Direct medical costs	Fixed and variable costs associated directly with a health care intervention (e.g., physician salaries)

Direct nonmedical cost	Nonmedical cost associated with provision of medical services (e.g., transportation of a patient to a hospital)
Discount rate	Rate of discount used to convert future costs and benefits into today's value; typically 2–6% per annum for costs and 0–6% for benefits
Effectiveness (of a drug)	Therapeutic outcome in a real world patient population (usually differs from efficacy determined in controlled clinical trials)
Formulary	List of drugs reimbursable under a health insurance plan or offered under a capitated or managed health care program or preferred in a particular clinical setting
Human capital method	Means of calculating the indirect cost of medical illness, based on the remaining economic value to society of a healthy individual of that age, measured by market earnings
Incremental cost	Difference between the cost of a program (treatment) and the cost of the comparison program
Indirect cost	Cost of reduced productivity resulting from illness or treatment (may be estimated by loss of wages and other means)
Intangible cost	Cost of pain and suffering occurring as a result of illness or treatment
Marginal costs	Extra cost of one extra unit of food product or service delivered (usually differs from average cost) (see also Average cost)
Markov model	Statistical representation of recurrent events over time that can be incorporated into decision analysis.
Net benefit	Benefit (in pecuniary units) minus total cost (in pecuniary units): a basic decision criterion in CBA
Opportunity cost	Cost of using resources for some purpose, measured as their value in their next alternative use
Sensitivity analysis	Process through which the robustness of an economic model is assessed by examining the changes in results of the analysis when key variables are varied over a specific range

Source: Richards et al. 1999.

Key Pharmacoeconomic Constructs: Costs, Perspective, and Sensitivity Analysis

Measuring Costs

In health economics, costs represent the value of a resource that is lost or used up as a consequence of an illness. Costs are traditionally divided into three types: direct, indirect, and intangible. Direct costs are defined as those that are expended when resources are consumed to provide treatments and/or services for an illness. Direct costs are often further divided into two categories: direct medical and direct nonmedical. The former category describes such expenses as hospitalization, pharmaceuticals, diagnostic tests, and service providers' fees. The latter category, or nonmedical direct costs, represents items that are linked to a medical intervention such as transportation to the care, food, clothing, and special equipment installation fees.

Although these cost definitions appear simple, interesting issues arise in specifying costs. One such issue is costs versus charges. In lay terms, the words "cost," "charge" and "price" are used interchangeably. Because buyers and sellers in health care operate from exceedingly different perspectives, they often do not have consensus on the value of a service or procedure. Hence, charges represent the amounts service providers—individuals or institutions (e.g., hospitals)—bill patients and insurers. Charges, therefore, do not exactly represent the actual value of the resources consumed to provide a service, but are described in the same units (i.e., monetary) as actual costs (Dranove 1995). Charges do not differentiate between a fixed and variable cost of the service. A fixed cost is not affected by the quantity of services provided, whereas a variable cost is. For example, a medication for an illness may increase or decrease the amount of blood work needed; the blood work is a variable cost since the amount required would change depending on the effect of the medication. The laboratory equipment to run the tests is seen as a fixed cost because it does not depend on the volume of service. In the relatively short run, the equipment will remain there, used more or less, and is not affected by the amount of blood work tests needed for that medication.

Indirect costs are resources that are lost, not directly expended, due to illness. As indicated in the introduction, neuropsychiatric disorders exert a profound toll on disability. Most indirect costs involve time or productivity in activities such as employment—of both the afflicted individual and his or her family and friend caretakers. Illness morbidity and mortality can result in disability days, lost days from work, decreased income (present and future), and even changed employment type. The methodology for calculating indirect costs is complex and is informed by two approaches: the human capital (HC) and willingness to pay (WTP) approaches (Dranove 1995).

The different types of costs to be measured for these analyses were described above. However, costs can be measured in different ways, are dependent on perspective, and have different underlying methodological assumptions. Wolff et al. (1997) outlined these complexities in an aptly titled paper “Getting the Cost Right in Cost Effectiveness Analysis,” highlighting the four potential areas that may bias cost estimates: study perspective, definition of the opportunity cost of resources, cost allocation rules, and measurement of service units. While a detailed discussion of these four areas is beyond the scope of this chapter, the authors cite important implications for both research and policy. The first issue is disclosure of methods—a theme echoed above and the reason behind the Panel on CEA. Important methodological information is not required in reports of analyses. Clearly the accuracy of cost estimates is crucial if such analyses are to be used for resource allocation or health care programming, yet using unit cost estimates (an ideal) does not necessarily mean that service or interventions are carefully or truly valued.

Finally, cost estimates often need to be adjusted for various reasons in order to offer meaningful comparisons across settings and time. Since inflation changes the value of the dollar over time, standard inflation or price indices are used to adjust costs in different years of a study. An example of such an adjustment is by use of the Medical Care Price Index, a subindex of the Consumer Price Index. A second issue that bears consideration is regional variation of costs, especially in multisite studies. Last, a technique known as discounting adjusts future costs to their contemporary value. Not only does the value of money change over time, but decisions to choose or delay certain outcomes in the future need to be factored in cost analyses. Standard discount rates are used for studies that go beyond a one-year time frame, and such a standard is 5–6% for developed nations (Viscusi 1995).

The human capital approach equates morbidity and mortality with lost wages or an individual’s economic productivity. This approach uses units that are of common interest and understandable to diverse constituents such as governments and employers and uses the prevailing wage rate for employment or an imputed rate for noncompetitive productive activity. Notable disadvantages of the human capital approach are the lack of a theoretical foundation, the lack of connection between market wages and an individual’s productivity, and the overvaluation of some groups’ productivity (e.g., employed Caucasian men vs. elderly, young, or nonwhite men and women).

The willingness-to-pay approach attempts to overcome the shortcomings of the human capital approach. This approach attempts to estimate how much an individual would pay to improve his or her welfare by avoiding an illness or disability. This approach hypothetically allows for the incorporation of indirect or intangible costs such as pain, suffering, or grief. Willingness-to-pay estimates

can be derived from indirect evidence of individuals' preferences or by direct elicitation of people's stated preferences. However, important issues to consider in deriving willingness-to-pay values include the use of hypothetical scenarios, baseline wealth, beliefs about risk and uncertainty, and actual experience with the illness or disability (Viscusi 1995; Pauly 1995).

Perspectives

While the societal perspective is seen as the gold standard for cost-effectiveness analysis, multiple stakeholders make up society, and their perspectives are worth thinking about and sometimes using in cost analyses. These stakeholders include patients, family members, providers, payers, employers, and others. Interesting stakeholder issues include:

1. Who are the stakeholders?
2. What preferences should be elicited and for what conditions?
3. Should different stakeholders' preferences be aggregated, and, if so, how?
4. When and at what levels should preferences be included in decision making?
5. Is there such a thing as an "unacceptable" preference? How should preferences be rejected?
6. Is consulting the public about health care priorities rational and/or ethical?

The Panel on CEA recommended a societal perspective because societal resources are finite, and argued that health should be subjected to the limitations that other social programs are (Gold et al. 1996). The Panel argued along many lines, including philosophical ones, and noted that "the societal perspective does not represent the situation from the viewpoint of particular agents in society, but it is the only perspective that never counts as a gain what is really someone else's loss. Beyond the philosophical arguments in its favor, there is value in beginning with a perspective that includes all costs and effects because it provides a background against which to assess results from other perspectives."

Conducting pharmacoeconomic analyses from more than one perspective can be very helpful (Detsky 1994; McGhan and Briesacher 1994). Given the attention paid to new pharmaceuticals, consider cost analyses from the following perspectives. A new medication is not on the formulary of a patient's health plan. The doctor's perspective is that this new, more costly medication is best for the patient due to minimal side effects with equal, if not better therapeutic efficacy, which may enhance adherence. From the patient's perspective, monetary cost is

critically important, since the patient will have to pay out of pocket for this new agent. Which perspective should guide the analysis of this medication?

Outcomes

The consideration and measurement of outcomes in pharmacoeconomics studies is critically important, especially for neuropsychiatric agents, given the complexity of mental health outcomes. The field has moved to utilizing a broader range of outcomes—not just mortality (which may not be a priority in some disorders) or clinical symptom resolution, but also functioning outcomes. In the child and adolescent arena, measurement of outcomes is fraught with unresolved measurement issues given the potential multiple sources of data even just for symptom and functioning measures (e.g., child, parents, schoolteachers) and the consideration of developmental phases. Another challenge is the state of the field for child functioning measures (Canino et al. 1999).

Other challenges addressed by Hargreaves et al. include (1) the representativeness of samples, (2) the diversity of clinical settings and community contexts, and (3) the length of follow-up intervals (Hargreaves et al. 1998). The authors also address the complexity of outcome domains to select and offer a framework for outcome measurement in cost studies of mental health interventions. One example is the use of five outcome domains for the adult area: measures of specific symptoms and disorders, measures of functioning, measures of general health status, measures of quality of life, and measures of public safety and societal welfare. Clearly, child and adolescent research have not yet fully developed measures for such domains as quality of life.

Sensitivity Analyses

As has been noted, the precision of cost analyses depends on many assumptions, so an analysis of the impact of those assumptions on results is critical and is known as sensitivity analysis. The main analysis is often called the base case, and sensitivity analyses describe alternative cases if an assumption (e.g., range or value used for a variable such as cost of a pharmaceutical or life expectancy with treatment) changes (Gold et al. 1996). Sensitivity analysis offers three opportunities: (1) to demonstrate the independence or dependence of a result on particular assumptions, (2) to establish the minimum or maximum values of a variable that are necessary to affect a decision to accept or reject a service or treatment, and (3) to identify key clinical or economic uncertainties that need more study.

Recommendations for Reporting

The Panel of CEA recommended important features of an analysis that would be useful to report for potential users and highlight any unusual issues. Table 2 gives this reporting checklist.

TABLE 2 Reporting Checklist

1. Framework	Background of the problem General framing and design of the analysis Target population for intervention Other program descriptors (e.g., care setting, model of delivery, timing of intervention) Description of comparator programs Boundaries of the analysis Time horizon Statement of the perspective of the analysis
2. Data and Methods	Description of event pathway Identification of outcomes of interest in program Description of model used Modeling assumptions Diagram of event pathway/model Software used Complete information on the sources of effectiveness data, cost data and preference weights Methods for obtaining estimates of effectiveness, costs, and preferences Critique of data quality Statement of year of costs Statement of method used to adjust costs for inflation Statement of type of currency Source and methods for obtaining expert judgment Statement of discount rates
3. Results	Results of model validation Reference case results (discounted and undiscounted); total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios Results of sensitivity analysis Other estimates of uncertainty, if available Graphical representation of C/E results Aggregate cost and effectiveness information Disaggregated results, as relevant Secondary analyses using 5% discount rate Other secondary analyses, as relevant
4. Discussion	Summary of reference case results Summary of sensitivity of results to assumptions and uncertainties in the analysis Discussion of analysis assumptions having important ethical implications Limitations of the study Relevance of study results for specific policy questions or decisions Results of related CEAs Distributive implications of an intervention

Source: Gold et al. 1996.

CHILDHOOD MENTAL DISORDERS COSTS, CONTEXTUAL INFLUENCES AND COST APPLICATIONS

Clearly the disease burden and costs of mental disorders in children and adolescents are just beginning to be fully appreciated. New evidence supports psychopharmacological treatments, but more evidence on the other dimensions of impact of pharmacological agents, such as cost-effectiveness, is needed (Sturm et al. 2001). However, beyond cost-effectiveness, some new work demonstrates how other cost issues need to be considered as prescribing increases, but the role of contextual factors has not been addressed much at all.

First, data indicate that rates of psychotropic prescribing for young children have risen, but little is known about the reasons why (Zito et al. 2000). Another recent study indicated that stimulants are prescribed for children and adolescents who do not meet criteria for either ADHD or ADHD-NOS, and some interesting characteristics such as gender, poverty, and ethnicity are associated with such observations (Angold et al. 2000). Finally, two studies (Kelleher et al. 2001; Leibson et al. 2001) have documented the costs associated with ADHD. These studies found that children with ADHD have higher medical care utilization and cost more than children with asthma. Little work exists on similar issues regarding specific disorder such as costs of adolescent depression, but some new work tries to capture the broader scope of psychotropic prescribing costs for children (Stein et al. 2001). Issues such as provider specialty and practice characteristics associated with psychotropic prescribing for children and associated costs are just beginning to be examined. As in the adult literature, prescribing, appropriate or not, is a complex process, and the numerous contextual influences on this process need to be kept in mind when doing this research (Hohmann 1999).

Much more research is needed in the area of costs of treatments for children and adolescents with mental disorders. This research, however, should ask Berger's question: How can CEA find greater use in the marketplace? In his 1999 article, Berger bemoans the lack of use of cost analyses, specifically CEA, by managed care organizations or public officials despite general interest and high promotion by researchers and some policymakers. He cites important factors that obstruct the application of CEA:

1. Payers have not been able to deny coverage for potentially life-saving interventions that are not believed to be cost-effective (e.g., bone marrow transplantation for breast cancer).
2. Providers do not effectively implement some very cost-effective interventions, which suggests that their disease management targeting is not informed by cost-effectiveness.
3. Providers do not consider cost-effectiveness an important criterion in making formulary decisions.

4. Large purchaser/employers rank CEA behind other criteria in selecting health plans.

Berger's recommendations for the uptake of CEA into real-world real-time decisions are relevant to the area of child and adolescent mental disorders and, if considered early, may be able to forgo some of the problems to date.

Recognition that a cost-effectiveness ratio that is clearly either cost-effective or not does not simply dictate whether to adopt or implement a particular health care intervention; this is an important (though obvious) first step that should be understood by payers, providers, and patients. This understanding should expand into a social process that legitimizes resource allocation choices through various mechanisms:

By facilitating a dialogue between providers and enrollees, a shared deliberation could emerge in which those covered by a health plan have an opportunity to buy into resource allocation decisions.

[By] providing an appeals process [that] would extend these deliberations to ensure that justice is guaranteed for both provider and enrollee when there are disputes.

[By making] results of these deliberations could be made explicit in contracting with new enrollees, increasing the likelihood that the values of the plan and the enrollees are aligned.

The challenges to fully applying and using cost analyses in such important areas as childhood mental disorders and their treatments are also unique opportunities to reduce the disease burden incurred by a society and make a difference in the quality of life for these children and their caregivers.

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5

Clinical Pharmacology of Psychoactive Drugs in Childhood and Adolescence

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It has been estimated that up to 10% of children have a psychiatric disorder that could be responsive to pharmacotherapy (Riddle et al. 1998). The most common of these conditions are attention-deficit hyperactivity disorder, major depressive disorder, and anxiety. Although the past decade has seen the introduction of numerous psychoactive drugs for the treatment of these and other diseases, the safety and efficacy of these drugs has generally not been studied in children. The lack of testing requires clinicians to prescribe medications without an FDA-approved indication for use in the pediatric population. Several psychiatric drugs (fluoxetine, sertraline, methylphenidate) are among the most common drugs prescribed off-label (Riddle et al. 1998). Pharmacoepidemiological research also suggests that the concurrent use of more than one psychotropic medication is increasing in children, raising the possibility of hazardous drug interactions (Vitiello and Hoagwood 1997).

The effectiveness of drug therapy depends on the selection of the correct therapeutic agent as well as the choice of an appropriate dosing regimen. In children, determining the optimal dose and dosing interval is a challenge given the limited data on the differences in the pharmacokinetics of drugs related to age

and size. Children are not ‘‘miniature adults,’’ and failure to properly account for differences in drug disposition between children and adults can result in either toxicity or a lack of effectiveness in the pediatric population. This chapter will review the basic pharmacokinetic parameters and physiological processes that influence drug disposition, examine the developmental and age-related differences between children and adults, and discuss approaches to designing optimal dosing regimens of drugs in children.

ABSORPTION AND BIOAVAILABILITY

In children as well as adults, the most common route of administration for chronic dosing of drugs is by mouth. In order to exert an effect, psychoactive agents must pass from the gastrointestinal tract through the liver and into the systemic circulation for delivery to the central nervous system. There are a number of reasons why orally administered drugs fail to reach the systemic circulation (Fleisher et al. 1999). Some (e.g., penicillins, erythromycin) are acid-labile and degrade in the acidic environment of the stomach. Poor formulation can lead to reduced absorption if the dosage form does not release the active ingredient in a timely fashion. Dissolution of the drug molecule in gastrointestinal fluid is also a requirement for absorption. Food may enhance the dissolution of drugs through the presence of lipid in the meal (e.g., cyclosporine) or the delay in gastric emptying associated with eating (Fleisher et al. 1999). Dissolution may also be related to pH. The antifungal drugs ketoconazole and itraconazole are more efficiently absorbed under conditions of high acidity. Even if a drug possesses the requisite physical and chemical characteristics for absorption, there is no guarantee of systemic availability. Cytochrome P450 enzymes in the gut wall and liver, particularly CYP3A4, can extract a substantial fraction of absorbed drug (Hall et al. 1999). In addition, P-glycoprotein, the product of the MDR1 gene, is expressed in high concentration in the enterocyte and transports substrates such as cyclosporine and verapamil back into the intestinal lumen (Stein 1997; Hall et al. 1999).

The pharmacokinetic parameter F represents bioavailability and is defined as the fraction of an orally administered dose that reaches the systemic circulation relative to an intravenous dose. This parameter is not always known for drugs lacking an intravenous formulation. The relationship between absorption, first-pass metabolism, and bioavailability is given by the following equation:

$$F = f_a \times (1 - E) \quad (1)$$

where f_a is the fraction of the dose absorbed from the gut and E is the extraction of drug by gut wall or liver on the first pass through these organs. Psychoactive drug molecules are characterized by high lipophilicity. The extent of absorption is usually complete, although the rate of absorption may be limited by slow disso-

lution. Bioavailability is frequently low due to extensive first-pass metabolism of drugs such as chlorpromazine, thioridazine, fluphenazine, haloperidol, moclobemide, protriptyline, imipramine, nefazodone, buspirone, paroxetine, fluoxetine, and sertraline (Balant-Gorgia et al. 1993; Mayersohn and Guentert 1995; Green and Barbhuiya 1997; Fand and Gorrod 1999; Devane 1999; Mahmood and Sahajwalla 1999). Although studies are limited, trifluoperazine, fluphenazine, chlorpromazine, and amitriptyline may also be substrates for P-glycoprotein (Stein 1997). There are few significant interactions between psychoactive drugs and food, although plasma concentrations of buspirone are doubled after a meal presumably due to reduced first-pass metabolism (Mahmood and Sahajwalla 1999).

DISTRIBUTION

The distribution of a drug in the body is primarily influenced by its chemical characteristics as well as binding to plasma proteins. The volume of distribution (V) is the pharmacokinetic parameter used to measure drug distribution. It is defined as the ratio of the amount of drug in the body to the concentration in the blood. After intravenous administration, V can be calculated using the following equation:

$$V = \frac{\text{Dose}}{C_{\text{peak}}} \quad (2)$$

where C_{peak} is the maximum plasma concentration achieved. The volume of distribution can be infinitely large and does not correlate to a real physiological space. It simply reflects the tendency of a drug to remain in or leave the blood. Drugs may be bound to proteins in plasma with albumin being the most important binding protein due to its high concentration (4–5 g/100 mL) as well as affinity for binding both acidic and basic drugs. α_1 -Acid glycoprotein also contributes to the binding of many basic drugs. Despite a high degree of plasma protein binding, many antipsychotic and antidepressant drugs have a large volume of distribution related to their high lipophilicity and affinity for tissue-binding sites. For example, the selective serotonin reuptake inhibitor, fluoxetine, has a volume of distribution of 1500–2000 liters in adults (Devane 1999).

METABOLISM

General Concepts

Drug metabolism can be broadly classified into Phase I and Phase II reactions. Phase I metabolism involves the formation of a more polar metabolite by oxidation, reduction, or hydrolysis of the parent compound. In a Phase II reaction,

drugs are conjugated with endogenous substrates such as sulfate, acetate, and glucuronic acid. Drugs may be subject to sequential metabolism whereby the introduction of a functional group (e.g., hydroxyl) in a Phase I reaction makes the molecule more amenable to secondary conjugation by Phase II enzymes. Metabolism does not always result in a less active species. Many psychotherapeutic agents have active metabolites including fluoxetine (norfluoxetine), citalopram (mono-desmethylcitalopram), imipramine (desipramine), amitriptyline (nortriptyline), thioridazine (mesoridazine), and risperidone (hydroxyrisperidone).

Although Phase II processes such as glucuronidation are important for the ultimate elimination of many antidepressant and antipsychotic drugs, the primary metabolic pathway is typically a Phase I reaction mediated by one or more of the cytochrome P450 enzymes. The cytochrome P450 system consists of a number of related families and subfamilies of enzymes that differ in terms of substrate specificity, polymorphic expression in the population, and susceptibility to inhibition and induction (Slaughter and Edwards 1995; Leeder and Kearns 1997; Oesterheld and Shader 1998). These enzymes have a dual physiological purpose. They are important in the synthesis and degradation of endogenous compounds (e.g., steroids) and serve a protective function in detoxifying foreign compounds, including drugs. The characteristics of the most important P450 enzymes involved in drug metabolism are listed in Table 1. These enzymes are present in a number of tissues throughout the body, including the liver, intestine, lungs, kidney, brain, adrenals, ovaries, and testes. Expression is greatest in the liver where enzymes of the CYP3A subfamily, particularly CYP3A4, are most abundant. CYP3A4 is responsible for the metabolism of the largest number of identified drug substrates and accounts for 30–40% of the total cytochrome P450 content of the liver and more than 70% in the intestine (Watkins et al. 1987; Shimada et al. 1994).

Pharmacogenetics of Drug Metabolism

The pharmacogenetics of these enzymes is of clinical importance in the field of psychiatry due to the large number of drugs metabolized by CYP2C19 and CYP2D6. Mutated alleles for these enzymes occur with varying frequency in different ethnic groups resulting in a polymorphic distribution of enzyme activity in the population (Caraco 1998; Daly et al. 1998; Coutts and Urichuk 1999; Ingelman-Sundberg et al. 1999). Patients with at least one wild-type allele coding for the fully functional protein are typically classed as extensive metabolizers, while those homozygous for mutated alleles are poor metabolizers. A difference of a single amino acid can, in some cases, produce an inactive protein. With CYP2C19, two mutations account for the vast majority of poor metabolizers. CYP2C19_{m1} is found in Caucasians, Africans, and Asians, while the CYP2C19_{m2} allele occurs almost exclusively in Asians and accounts for the higher incidence

TABLE 1 Characteristics of the Primary Cytochrome P450 Enzymes Involved in Metabolism of Psychoactive Drugs^a

Enzyme	% of total P450 in adult liver	Polymorphic expression	Selected substrates	Inhibitors
CYP1A2	15–20	No	Caffeine, theophylline, R-warfarin, amitriptyline, fluvoxamine, clozapine	Ciproflaxacin, erythromycin, amiodarone, fluvoxamine
CYP2C9	15–20	<0.5% poor metabolizer's (PMs)	Tolbutamide, phenytoin, S-warfarin, diclofenac, naproxen, ibuprofen, fluoxetine, fluvoxamine	Sulfaphenazole, cimetidine, fluvoxamine, fluoxetine
CYP2C19	1	Caucasians: 1–3% PMs African: 1–3% PMs Asian: 15–20% PMs	S-Mephenytoin, omeprazole, diazepam, imipramine, citalopram, moclobemide, amitriptyline, clomipramine	Fluvoxamine, moclobemide
CYP2D6	1–3	Caucasians: 5–10% PMs African: 1–8% PMs Asian: 1–3% PMs	Debrisoquine, dextromethorphan, propranolol, codeine, propafenone, amitriptyline, nortriptyline, imipramine, desipramine, haloperidol, fluoxetine, paroxetine, venlafaxine, risperidone, thioridazine, perphenazine, mianserin, citalopram	Quinidine, haloperidol, fluoxetine, norfluoxetine, paroxetine, moclobemide
CYP3A4	30–40	No	Testosterone, ethinylestradiol, cyclosporine, carbamazepine , erythromycin, indinavir, saquinavir, ritonavir, lovastatin, quinidine, terfenadine, nifedipine, diltiazem, verapamil, midazolam, triazolam, nefazadone, mirtazapine, sertraline, buspirone	Ketoconazole, itraconazole, erythromycin, verapamil, diltiazem, grapefruit juice, amiodarone, indinavir, ritonavir, clarithromycin, nefazadone, hydroxynefazadone, norfluoxetine, fluvoxamine

^a Psychoactive agents in bold.

of poor metabolizers in this population (Table 1) (de Morais et al. 1994). Numerous mutated alleles have been identified for the CYP2D6 enzyme (Masimirembwa and Hasler 1997; Coutts and Urichuk 1999). In Caucasians, the most common defective allele is CYP2D6B, a mutation that occurs less frequently in African Americans and is not found in Asians. The overall frequency of defective alleles is approximately 25–30% in Caucasians resulting in 5–10% of the population being homozygous for the poor metabolizer phenotype. In Asians, poor metabolizers for CYP2D6 are much less common at less than 2%. Conflicting results have been reported in patients of African descent and may reflect differences between populations originating from different regions within Africa (Masimirembwa and Hasler 1997). Although the overall frequency of the poor metabolizer phenotype appears to be lower than in Caucasians, some mutant alleles such as CYP2D6*17 occur uniquely in Africans (Masimirembwa et al. 1996). The clinical consequence of the polymorphic expression of these enzymes is not always easy to predict. Certainly, poor metabolizers will exhibit lower clearance and higher plasma concentrations of drugs metabolized primarily by these enzymes. The area under the plasma concentration-time curve (AUC) of drugs such as desipramine, thiordiazine, fluoxetine, perphenazine, and paroxetine is typically 3- to 6-fold higher in poor metabolizers given the same dose as extensive metabolizers (Masimirembwa and Hasler 1997). In one study, the half-life of fluoxetine averaged 76 hours in poor metabolizers compared to 24 hours in phenotypic extensive metabolizers (Hamelin et al. 1996). When the pharmacological effect of a drug is primarily due to the parent compound, poor metabolizers may be more susceptible to adverse reactions due to the achievement of higher plasma concentrations. This has been documented with nortriptyline as well as in patients receiving neuroleptics (Bertillon et al. 1982; Spina et al. 1994). However, many antidepressants and antipsychotics have active metabolites that make a substantial contribution to the effects of the drug. While poor metabolizers have high concentrations of parent compound and little metabolite, extensive metabolizers will have low concentrations of the parent and substantial amounts of active metabolites, making it difficult to predict the overall consequence to the patient. Complicating the assessment is the fact that the rate of drug metabolism can vary widely even within a group of patients phenotyped as extensive metabolizers. Patients who are heterozygous with one wild-type allele and one mutated allele may metabolize substrates at an intermediate rate. In addition, a small sub group of ultrarapid metabolizers for CYP2D6 has been identified. This phenomenon has only been observed in Caucasians and appears to be due to amplification or duplication of a functional allele (CYP2D6L) (Bertillon et al. 1993). Ultrarapid metabolizers have been demonstrated to have extremely high dose requirements of antidepressants such as nortriptyline (Bertillon et al. 1997). Due to the large number of psychoactive drugs metabolized by CYP2D6, screening patients for

enzyme activity has been suggested as a potentially cost-effective procedure to provide more optimal drug treatment (Chen et al. 1996).

Metabolic Drug Interactions

Inhibition or induction of the activity of the cytochrome P450 enzymes can result in clinically important drug interactions. The most common inducers of metabolism are the anticonvulsant drugs phenytoin, phenobarbital, and carbamazepine along with the antibiotic rifampin. These compounds tend to induce a broad range of P450 enzymes resulting in increased protein concentration that is maximal 2–4 weeks after starting therapy with the inducer. Induction of metabolism results in increased clearance as well as decreased oral bioavailability of drugs subject to first-pass metabolism. This has the potential to render psychotherapeutic agents ineffective when the effect of the drug is primarily due to the parent compound. Perhaps a more significant cause of drug interactions in psychopharmacology is inhibition of metabolism (Ten Eick et al. 1998; Jefferson 1998; Greenblatt et al. 1998). A large number of psychoactive drugs have been identified as inhibitors of cytochrome P450 enzymes. Inhibition can be clinically evident even after the first dose and is a primary concern when inhibitors are co-administered with drugs having a narrow therapeutic range that children may be taking. The selective serotonin reuptake inhibitors (SSRIs) are attractive choices for the treatment of childhood depression due to their favorable side effect profile relative to the older antidepressants. However, many of these compounds are potent inhibitors of specific P450 enzymes (Table 1). Fluvoxamine inhibits CYP1A2 activity and would be expected to increase plasma concentrations of theophylline. Inhibitors of CYP2C9 such as fluvoxamine and fluoxetine are a concern in patients taking phenytoin or warfarin. Paroxetine and fluoxetine along with the antipsychotic haloperidol and the MAO-A inhibitor moclobemide decrease CYP2D6 activity. Excessive sedation and extrapyramidal symptoms associated with up to 20-fold increases in plasma concentrations were observed in subjects given perphenazine in combination with paroxetine (Ozdemir et al. 1997). Since genetically poor metabolizers do not have a functional form of the enzyme, inhibitors of CYP2D6 are not a concern in this sub population. CYP3A4 is responsible for metabolism of the broadest range of drugs. Inhibition by ketoconazole, itraconazole, diltiazem, erythromycin, clarithromycin, and grapefruit juice has resulted in serious and occasionally fatal cardiovascular toxicity with drugs such as cisapride and the non-sedating antihistamines terfenadine and astemizole. Plasma concentrations of buspirone, midazolam, and triazolam are increased more than 10-fold when co-administered with potent inhibitors such as ketoconazole and itraconazole (Olkola et al. 1994; Varheetal 1994; Kivisto et al. 1997). Nefazodone and fluoxetine also inhibit CYP3A4 and should be administered with caution in children receiving

drugs metabolized by this enzyme. Of the SSRIs, citalopram appears to have the least propensity to inhibit cytochrome P450 activity and may be preferred in patients where drug interactions are a significant concern.

ELIMINATION

Elimination of drug from the body is primarily due to metabolism in the liver or excretion into the urine. Renal clearance is the net effect of filtration of the drug at the glomerulus plus active tubular secretion minus any reabsorption of the drug from the urine back into tubular cells and ultimately the plasma. Factors such as lipophilicity of the drug molecule, degree of plasma protein binding, molecular size and urinary pH can influence renal elimination of drug. Most psychoactive drugs are lipophilic and highly bound to plasma proteins resulting in limited glomerular filtration and efficient reabsorption. As a result, these drugs require metabolism to more polar compounds in order to be efficiently eliminated from the body.

The pharmacokinetic parameters clearance (Cl), elimination rate constant (k) and elimination half-life ($t_{1/2}$) can be used to characterize different aspects of drug elimination. Clearance refers to the volume of plasma from which drug is irreversibly removed per unit time. It is the product of blood flow to the clearing organ (Q) and the extraction of the drug (E) by the clearing organ:

$$Cl = Q \times E \quad (3)$$

Clearance can be thought of as representing the efficiency of the clearing organs in cleansing the blood of drug. The maximal value for clearance is equal to the blood flow to the clearing organ (approximately 1.5 and 1.25 L/min for hepatic and renal clearance, respectively). Since clearance is expressed in units of volume per time, this parameter does not measure the amount of drug eliminated.

The elimination of most drugs occurs by a first-order process where the rate of elimination is proportional to the concentration of drug. Elimination is faster at higher concentrations and slower at low concentrations, producing a non linear relationship between plasma concentration and time when drugs are administered as an intermittent bolus. Increasing the dose results in a proportional increase in rate of elimination and concentration of drug in the body. Notable exceptions to the common pattern of drug elimination are phenytoin and ethanol. Dose-dependent elimination has also been reported for moclobemide (Mayersohn and Guentert 1995) and several SSRIs (fluoxetine, fluvoxamine, paroxetine) (Devane 1999). The clinical significance of this phenomenon over the range of doses used in patients is unclear.

The elimination rate constant (k) refers to the fraction of the amount of drug in the body eliminated per time. Even though the amount of drug eliminated via a first-order process over a specific period of time is dependent on the amount

in the body, the fraction eliminated remains constant. Since half-life is also a fraction (the time required for half of the drug to be eliminated or for plasma concentrations to decline by 50%), it is related to the elimination rate constant by the following equation:

$$t_{1/2} = \frac{0.693}{k} \quad (4)$$

Elimination rate constant and half-life of a drug are dependent on both the clearance and volume of distribution:

$$k = \frac{Cl}{V} \quad (5)$$

$$t_{1/2} = \frac{0.693 \times V}{Cl} \quad (6)$$

When the clearance is high, the elimination rate constant will be larger and half-life shorter. Conversely, when a drug has a large volume of distribution, elimination will be slow since only a small fraction of the drug in the body will be present in the blood where clearance and elimination of drug takes place. Despite the fact that the clearance of many psychoactive drugs is high, half-life is frequently long due to the large volume of distribution that these drugs tend to exhibit.

EFFECT OF DEVELOPMENT ON DRUG DISPOSITION IN CHILDREN

At birth, gastric pH is high, gastric emptying is slow, and intestinal motility is reduced. Both rate and extent of absorption of drugs is unpredictable in neonates and varies widely from drug to drug. However, these processes develop rapidly over the first year of life, and by the age of 3 years it is generally assumed that the bioavailability of drugs in children is comparable to that observed in adults (Koren 1997). Infants have a higher percentage of body weight as total body water (75% vs. 55%) and extracellular fluid (40% vs. 20%) than adults. They also have less fat, less muscle, and somewhat lower (20%) concentrations of albumin, the primary drug-binding protein (Koren 1997). This may result in a higher volume of distribution for water-soluble drugs such as gentamicin and for drugs highly bound to plasma proteins. While potentially important in young infants, differences in distribution from adults are likely to be of little clinical significance in older children.

Given the role of drug metabolism in the elimination of psychoactive drugs, the ontogeny of the P450 enzymes is of considerable interest (Cresteil 1998). At birth, concentrations of most of the important drug-metabolizing enzymes are

extremely low, while CYP3A7, found in high concentrations in fetal liver and primarily responsible for the metabolism of endogenous steroids, is the predominant P450 enzyme. The CYP2C9, CYP2D6, and CYP3A4 enzymes surge immediately after birth, and by the age of 1 month concentrations approach 20–30% of adult values. The development of CYP1A2 is somewhat delayed accounting for the prolonged half-life of substrates such as caffeine in neonates. The cytochrome P450 enzymes continue to develop during the first year of life, at which time adult values are approached. Phase II enzymes show considerable variability in the degree of expression at birth. Sulfation appears to be relatively active, while glucuronidation of many substrates is significantly impaired. The presence of numerous isoforms of glucuronosyltransferase with overlapping substrate specificity makes it difficult to draw general conclusions concerning the development of glucuronidation (de Wildt et al. 1999). However, it appears safe to assume that full maturity of these enzymes is reached by 3–4 years of age. Renal function at birth is approximately one-third that of an adult with filtration developed to a somewhat greater extent than secretion. Glomerular filtration rate increases rapidly in the first month of postnatal life and reaches adult values (when normalized for body surface area) by the age of one. The vast majority of psychoactive drug usage in the pediatric population occurs in children over the age of 5 years. By this age, it can be assumed that the basic physiological processes that govern drug disposition are reasonably mature.

DOSING CONSIDERATIONS FOR PSYCHOACTIVE DRUGS IN CHILDREN

Dosing strategies with chronic administration of drugs revolve around attempting to achieve and maintain the concentration of drug in plasma within a range known to be associated with beneficial therapeutic effects and minimal toxicity. The average drug concentration with chronic administration under steady-state conditions is given by the following equation:

$$C_{ss,av} = \frac{F \times \text{Dose}}{Cl \times \tau} \quad (7)$$

where τ is the dosing interval. Unfortunately, there is little information specific to the pediatric population concerning the relationship between drug concentration and effect. For many drugs, it is assumed that this relationship is similar in children and adults so that the target drug concentration to be achieved will be the same irrespective of the age of the patient. Since drug bioavailability in children is generally comparable to that in adults, inspection of Eq. (7) indicates that the primary challenge in selecting a dose will be accounting for any differences in clearance between children and adults.

Although the physiological processes responsible for drug clearance will be mature in a school-aged child receiving treatment with psychoactive medication, the absolute value for drug clearance will typically be smaller due to the size difference between children and adults. The daily dose requirement in a child relative to a healthy adult can be calculated according to the following formula:

$$\text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} \times \frac{\text{Cl}_{\text{child}}}{\text{Cl}_{\text{adult}}} \quad (8)$$

A critical question relates to how size differences between adults and children should be measured. A typical 7-year-old child weighs about 23 kg or approximately one third of a standard adult weight of 70 kg. On the other hand, the same child will be roughly 120 cm tall or close to two-thirds adult height. It is evident that reducing drug dosage on the basis of weight is not an appropriate dosing strategy in children. Findling et al. (1999) studied the pharmacokinetics of paroxetine in children and adolescents and found clearance per kg to be much faster than adult values. This is consistent with other studies that have consistently reported that the clearance of drugs adjusted for body weight is often twice as high in children relative to adults (Renwick 1998). The physiological basis for this may be partially related to the fact that clearing organs such as the liver and kidney represent a higher fraction of body weight in children than they do in adults. An alternative and widely used approach is to adjust dosing in children on the basis of body surface area. Surface area (SA) is a function of both the height (Ht) and weight (Wt) of the child, and many formulas have been developed to calculate this parameter, including the classic Du Bois equation (Du Bois and Du Bois 1916):

$$\text{SA} = 0.00718 \times \text{Ht}^{0.725} \times \text{Wt}^{0.425} \quad (9)$$

Surface area can also be approximated using a simplified equation as follows:

$$\text{SA} = \frac{(\text{Ht} \times \text{Wt})^{1/2}}{60} \quad (10)$$

where height is measured in cm and weight in kg. It should be noted that the Du Bois equation was intended to estimate the surface area of the skin and does not necessarily approximate the surface area of key internal organs involved in drug clearance. Nonetheless, the adjustment of drug dosage on the basis of surface area is superior to the use of body weight alone. Drug clearance normalized for surface area has been found to be relatively similar in children and adults for a wide range of drugs (Edwards and Stoeckel 1992).

The science of allometrics relates differences in body size to body function and is widely used in cross-species scaling. These principles have been applied to the problem of drug clearance in children (Holford 1996; Anderson et al. 1997)

and suggest that the clearance of a child can be related to that of an adult using the following equation:

$$Cl_{\text{child}} = Cl_{\text{adult}} \times \left(\frac{W_{\text{tchild}}}{W_{\text{tadult}}} \right)^{3/4} \quad (11)$$

This equation is known as the 3/4-power law and appears to accurately predict drug clearance over a wide range of body weight. It is likely that the difference in predicted clearance between this model and the surface area model will be minimal in children over the age of 5 years.

Although the total daily dose requirement in a patient is a function of the clearance [Eq. (7)], the dosing interval is related to the half-life. As previously discussed, half-life is dependent on both the clearance and volume of distribution [Eq. (6)]. It has been well documented that the half-life of many drugs is shorter in children than in adults. A simplistic but useful explanation for this phenomenon is that while clearance in a child correlates with body surface area, volume of distribution is related to body weight. Since the ratio of surface area to weight is roughly 50% higher in a 6-year-old child than in an adult (Renwick 1998), the absolute value for clearance in children is closer to the adult value than is the volume of distribution. The shorter half-life necessitates the administration of drugs with a narrow therapeutic range at more frequent intervals in children.

SUMMARY

It is evident from this discussion that appropriate dosing of psychoactive drugs will require an understanding of pharmacokinetic parameters such as clearance and half-life, routes of elimination, specific cytochrome P450 enzymes involved in metabolism, and the physiological and developmental differences between children and adults in drug disposition. It is unfortunate that pharmacokinetic information as well as concentration-response data are often not available for the pediatric population and must be extrapolated from adult studies. Recent initiatives by the U.S. Food and Drug Administration and the National Institutes of Health have provided incentives for researchers to include children in clinical drug research. However, in view of the limitations of the data currently available and the potential problems related to polymorphic metabolism, drug interactions and lack of a defined target plasma concentration, children being treated with psychoactive medication should be closely monitored.

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Cardiac Side Effects of Psychotropic Medications in Children and Adolescents

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INTRODUCTION

Over the last two decades there has been a steady increase in the use of psychotropics in children for various psychiatric disorders. Previously, usage was limited to psychostimulants and antipsychotics for conditions such as attention deficit disorder and childhood psychoses. However, in recent years, depressive and anxiety disorders have been diagnosed in children and adolescents more frequently and pharmacological treatment with various antidepressants and anxiolytics has become more acceptable. The increasing use of these medications has also necessitated more awareness of various side effects of these drugs.

Children have a reduced capacity for albumin binding and a smaller adipose compartment, resulting in higher levels of unbound compounds than adults. Children also have a quicker biotransformation of drugs in the liver, and this could result in shorter drug half-life and a greater chance for exposure to toxic metabolite levels. Renal clearance of drugs is also more rapid in children. These factors need to be taken into consideration while evaluating the drug effects and side effects in children (Rancurello et al. 1992).

Cardiovascular side effects are common with most psychotropics due to the autonomic effects associated with these agents. Though the usual side effects such as an increase in heart rate or small changes in blood pressure are of no serious concern during treatment, occasionally therapeutic doses of agents such as tricyclic antidepressants (TCAs) have resulted in sudden death (Riddle et al. 1991, 1993; Varley and McClellan 1997). The reason for this kind of adverse effect is not clear, and it is possible that in a child who has a pre existing cardiac problem such as a long QT interval, drugs like desipramine may prolong it further leading to conduction disturbances and severe ventricular arrhythmias, with a fatal outcome. Thus it is important to have a good understanding of the pharmacological profile of a drug and how it might affect an individual child. It is also important to understand the effects of toxic doses of these agents as attempted and accidental overdoses occur frequently with these agents.

NORMAL AND ABNORMAL CARDIOVASCULAR PHYSIOLOGY

The electrocardiograph (ECG) enables the physician to infer the course of cardiac impulse by recording the variations in electrical potential at various loci on the body surface (Berne and Levy 1986). This gives insight into the relative sizes of cardiac chambers, disturbances of cardiac rhythm and conduction, information of myocardial ischemic damage and the effects of pharmacological agents on the heart. In general, the ECG consists of P, QRS, and T waves. The PR interval is the time between the onset of atrial activation to the onset of ventricular activation. Normally the duration of the PR interval is 120–200 msec. The duration of QRS is between 60 and 100 msec, and abnormal prolongation may indicate a conduction disturbance in the ventricular pathways such as the left or the right bundle branch. Depolarization of the ventricular myocardium occurs during the ST interval, and usually the ST segment lies on the isoelectric line. QT interval is also referred to as the electrical systole of the heart and varies inversely with the heart rate. The usual duration is about 400 msec. Abnormal T waves in direction or amplitude may indicate different cardiac disease conditions.

Cardiac arrhythmias reflect disturbances of impulse initiation or impulse propagation. These consist of conduction blocks, reentrant rhythms, and dysfunction of sinoatrial (SA) node and disturbances that originate from various ectopic foci. Respiratory sinus arrhythmia (RSA) is common and results in sinus bradycardia or tachycardia, which is influenced by cardiac vagal function. First-degree atrioventricular (AV) block is characterized by a prolonged PR interval. In second-degree AV block, all QRS complexes are preceded by P waves but not all P waves are followed by QRS complexes due to the block. This type of block is more serious when the block occurs above the bundle of His. In third-degree AV block, there is complete heart block, and most common sites of these are

distal to the bundle of His. In this type of block, the atrial and ventricular rhythms are independent of each other. Because of the slow ventricular rhythm, there is inadequate blood supply, often associated with syncope (Adams-Stokes attacks) due to insufficient cerebral blood flow.

Premature systoles may originate in the atria, AV junction, or ventricles. They are sometimes coupled to normal beats, and sometimes not. In premature atrial systole, the configuration of the premature P wave is different from the normal P wave as the premature one originates at some ectopic focus in the atrium. This can lead to abnormal ventricular activation leading to abnormal configuration of the QRS complex. A premature ventricular systole can be due to a ventricular ectopic focus leading to a different configuration of QRS and T waves. The prolonged interval that follows a premature ventricular systole is known as the compensatory pause.

Tachycardia originating from an ectopic focus has an abrupt onset and termination compared to sinus tachycardia. Those are known as paroxysmal tachycardias. These that originate in the atria or AV junction are referred to as paroxysmal supraventricular tachycardias. This is associated with normal QRS complexes. However, when the tachycardia is excessively high, second-degree AV blocks may result. Paroxysmal ventricular tachycardia is the result of an ectopic focus in the ventricles and can be associated with bizarre QRS complexes in the ECG. This is much more serious than a paroxysmal supraventricular tachycardia since paroxysmal ventricular tachycardia could lead to ventricular fibrillation.

Fibrillation is an irregular contraction and is ineffectual in propelling blood. This could involve the atria or ventricles. In atrial fibrillation, there is a continuous uncoordinated rippling type of activity. The ECG contains no P waves. There is no constant interval between QRS complexes and therefore between ventricular contractions. Thus, the pulse is extremely irregular in regards to rhythm as well as force. In some cases, the atrial reentry loop and AV conduction are more regular, and this condition is referred to as atrial flutter. Atrial flutter and fibrillation may be compatible with life and full activity, but the onset of ventricular fibrillation leads to unconsciousness within a few seconds. This can potentially lead to death unless treated effectively. In the ventricles, the vulnerable period coincides with the down slope of the T wave, and when a premature impulse arrives during the vulnerable period, this may lead to fibrillation. This may become self-sustaining due to a reentrant process of cardiac excitability. Drugs that prolong the refractory period or a strong electric current (cardio version) that puts the entire myocardium briefly in a refractory state may revert atrial fibrillation.

Evaluation of cardiovascular function is relatively simple, and a routine clinical history and physical examination can identify conditions such as congenital heart disease, valvular disease, hypertension, and mitral valve prolapse. A 12-

lead ECG can identify any abnormalities in QRS or QT intervals or bundle branch blocks. In children, the supine heart rate (HR) is somewhat higher than in adults (Yeragani et al. 1994a, 1997). It is a good practice to have a baseline ECG for all children before they receive any medication with appreciable effects on the cardiovascular system so that the effects can be monitored in a meaningful fashion.

Preexisting medical conditions such as congenital long QT syndrome, congenital heart disease, and hypothyroidism and serum electrolyte disturbances deserve special mention. Because some psychotropics such as tricyclic antidepressants and antipsychotics, especially in higher doses, can result in prolonged QT interval, these should be used very cautiously in children with the above medical conditions.

CONGENITAL HEART DISEASE

While there is an exhaustive list of congenital defects that could affect the heart, some of these conditions may be symptomless in childhood and adolescence. A majority of these conditions could eventually lead to cardiac failure. Conditions causing left or right ventricular hypertrophy and failure may eventually lead to fatal arrhythmias if untreated. Also, patients with tetralogy of Fallot are especially vulnerable to cardiac arrhythmias in the postoperative period (Freedom and Nykanen 1998). Thus, psychotropic medication with autonomic side effects should be carefully used in this population, and the patients should be monitored for the development of any arrhythmias. This is especially important in relation to TCAs and anticholinergic medications. QTc prolongation is always more dangerous in the setting of a higher heart rate.

CONGENITAL LONG QT SYNDROME

The genetic long QT syndrome (LQTS), LQT1–6, is inherited as an autosomal dominant condition due to genetic mutations that encode for cardiac ion channels (Vincent 2000). The characteristic manifestations are prolongation of the QT interval and T-wave abnormalities on the ECG, syncope precipitated by exercise or emotional situations, and sudden death resulting from the ventricular tachyarrhythmia torsades de pointes (TDP). TDP, a paroxysmal ventricular arrhythmia, may be precipitated by drugs such as TCAs and antipsychotics that prolong QT interval, especially in the background of higher heart rates. Most often, TDP is self-terminating, causing a syncopal episode, which is followed by a quick recovery.

Acquired LQTS

There is a long list of drugs that can result in TDP in susceptible patients. Drugs cause TDP usually by blocking cardiac potassium channels. Because both drug-induced and LQT2 forms of LQTS are caused by the blockade of cardiac potassium channels, it is possible that drug-induced LQTS may be associated with underlying genetic predisposition. It is important to note that some LQTS gene carriers have normal to borderline QT intervals. It is possible that these subjects are especially vulnerable to the effects of drugs that prolong the QT interval. It is also noteworthy that hypokalemia and hypomagnesemia also can cause QT prolongation, T-wave abnormalities, and arrhythmias. Acquired LQTS is mainly associated with syncopal attacks, sometimes many per day. Jervell and Lange-Nielsen syndrome patients usually have the onset within the first few years, whereas Romano-Ward syndrome appears in the preteen to midteen years. Only one third of the gene carriers are symptomatic, and the rest may lead totally normal lives. As some reports suggest, seizures also occur in LQTS. Few deaths occur during sleep. The QTc averages 410–600 msec in LQTS. In one study, 5% of the gene carriers had a QTc of 440 msec, usually interpreted as normal, and another 30% between 450 and 470 msec. Thus, 35% of the QTc values fall in the nondiagnostic range. It is reported that a QTc interval of 470 msec in men and 480 msec in women was 100% sensitive for LQTS, and a QTc of <400 msec in men and <420 msec in women was 100% specific for excluding LQTS. In some, exercise testing shows an abnormal QT response, not in line with the decrement in cycle length. The common eventuality in all kinds of LQTS is prolongation of the action potential duration, which renders the myocytes vulnerable to early after depolarizations, which initiates TDP. Further discussion of the mechanism of arrhythmias in LQTS is beyond the scope of this chapter, and the readers are referred to the excellent review by Vincent (Vincent 2000).

Management of LQTS

Beta-blockers are the drugs of choice in the treatment of LQTS. This therapy is effective in up to 90% of patients, resulting in a decrease of the rate of sudden death. In high-risk patients, the implantable cardiac defibrillator may be of value. Another promising finding is that in LQT3, mexelitin, a sodium channel blocker, may shorten the QT interval. In LQT1, potassium channel openers may also be of value. In cases with LQTS, it is best not to use any drugs that may further prolong the QTc. In the treatment of depression or anxiety, serotonergic reuptake inhibitors (SRIs), which have a different cardiac side effect profile, may be preferable to TCAs.

Recent developments in investigative cardiology using noninvasive tools such as echocardiogram and quantification of HR and QT variability may be of

great value as baseline measures before a particular medication is started, especially in vulnerable groups.

VENTRICULAR ARRHYTHMIAS IN NORMAL HEARTS

Idiopathic ventricular tachycardia (IVT) belongs to this group and can be of multiple subtypes: adenosine-sensitive, verapamil-sensitive, and propranolol-sensitive. Some of these are catecholamine-dependent and thus need a special mention in reference to the use of psychotropics with noradrenergic effects such as TCAs. Exercise can induce VT in some of these patients. These are usually responsive to beta-blockers or calcium channel blockers or a combination of these drugs. For a review of this topic, the reader is referred to the article by Lerman et al. (2000).

MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP) is of special interest because of the reported association with anxiety disorders. A percentage of these children may need to be on psychotropic medication when other treatment modalities do not work.

The principal anatomic defect in MVP is a redundancy of myxomatous connective tissue of the mitral valve, mainly in the posterior leaflet. This causes the tissue to prolapse in to the left atrium during systole (Alpert et al. 1998). This defect may be idiopathic or may be secondary to other medical disorders such as Marfan's syndrome or ischemic heart disease. Midsystolic clicks or late systolic murmurs are usually associated with this condition. The clinical features can be diverse, including atypical chest pain, palpitations, endocarditis, and sometimes sudden death. MVP is usually diagnosed in about 5% of the healthy population and is more common in females. The prevalence of MVP can vary quite a bit depending on the diagnostic criteria on the echocardiography. MVP can occur in one setting, where there is an anatomical defect in the mitral valve leaflet, and in another, where it can be "functional," possibly due to decreased left ventricular size.

Some studies have estimated the incidence of MVP in patients with agoraphobia or panic attacks to be up to 50% (Kantor et al. 1980). This finding has been challenged by other investigators (Kathol et al. 1980). The majority of these patients with associated panic attacks respond well to the conventional tricyclics and SRIs. However, some of these patients also may benefit from beta-blockers for the symptoms of paroxysmal tachycardia often seen in MVP. It is always wise to monitor ECG during treatment with psychotropics in these patients, because some drugs like TCAs may cause unwanted side effects in this group.

Gorman et al. (1988) have reported that panic patients with and without MVP did not differ in their plasma epinephrine, norepinephrine, PR and QRS

intervals, and ventricular rate and blood pressure. However, there was a trend for the MVP patients to have a longer QTc. This should be kept in mind while using any medications such as TCAs that might adversely affect the QTc.

SYNCOPE

For a detailed discussion on this subject, the reader is referred to an excellent review by Benditt (1998). Syncope is the transient loss of consciousness as well as postural tone with a spontaneous recovery subsequently. Syncope results from a variety of conditions, and thus it is important to understand the etiology before starting treatment. The following conditions are usually associated with syncope: neurally mediated disturbances such as vasovagal and carotid sinus syncope, orthostatic and dysautonomic circulatory disturbances, cardiac arrhythmias and other cardiovascular and cerebrovascular conditions, and neurological and psychiatric disorders. In primary cardiac conditions and other neurological illnesses, treatment of the primary condition is sufficient to relieve syncope.

Neurally mediated syncope is associated with reflex disturbances of blood pressure control such as vasovagal faint, carotid sinus syncope, syncope related to cough, swallowing, defecation, micturition, and airway stimulation. Orthostatic and dysautonomic circulatory disturbances include idiopathic orthostatic hypotension, neurological conditions such as diabetic neuropathy, and, most relevant for this chapter, drug-induced orthostasis. The minimum cerebral oxygen delivery for the maintenance of consciousness is about 3.5 mL/100 g of brain tissue per each minute. In healthy individuals, these flows are typically 50–60 mL/min/100 g of tissue. These levels are achieved with little difficulty at various perfusion pressures. Baroreceptor-induced regulation of HR and systemic vascular resistance has a significant protective influence in this context.

In neurally mediated syncope, signals from the periphery trigger the events in the medullary cardiovascular control centers, causing afferent signals to cause bradycardic and vasodilatory response resulting in syncope. The susceptibility to these events may be associated with an increase in circulating levels of epinephrine, vasopressin, and beta-endorphins. Due to the declining systemic perfusion pressure, there may be excessive cerebrovascular constriction leading to syncope.

Orthostatic or postural hypotension is defined as a drop of about 20 mmHg of systolic blood pressure upon standing. This is associated with autonomic failure due to inadequate reflex adjustments to upright posture. In addition to primary autonomic failure and other medical conditions, drugs such as alcohol, major and minor tranquilizers, vasodilators, and antidepressants, especially TCAs, are usually the offending agents. This can lead to falls and fractures, which is an especially troublesome problem in the elderly. Monoamine oxidase inhibitors (MAOIs) can frequently cause this side effect, especially in combination with some antihypertensives. In this context, it is important to note a recent finding

of Grubb et al. (1994) that the selective serotonin reuptake inhibitor (SSRI), sertraline hydrochloride, is effective in preventing recurrent neurocardiogenic syncope that is not responsive to other treatment modalities. In this study, the age group was 10–18 years and there was no evidence of any heart disease. Eleven out of 17 patients experienced syncope during tilt-table testing. This suggests a role for serotonin in the regulation of vascular reflexes related to syncope.

HEART RATE OR HEART PERIOD VARIABILITY

Vagal as well as sympathetic systems contribute to HR variability (Akselrod et al. 1981; Pomeranz et al. 1985; Malliani et al. 1991). A decrease in HR variability is a robust predictor of cardiovascular mortality and sudden death in cardiac patients as well as normal controls (Molgaard et al. 1991; Bigger et al. 1992). Increased sympathetic activity or a decrease in vagal activity can tilt the sympatho-vagal balance and may result in significant cardiac events, even sudden death. Mean HR over a period of time gives only limited amount of information, whereas beat-to-beat HR time series over a period of time, say 5 minutes, can give more information. Spectral analysis using Fourier transform usually shows two peaks, one at LF (low frequency: 0.04–0.15 Hz) and one at HF (high frequency: 0.15–0.5 Hz). HF power is related to respiratory sinus arrhythmia (RSA), thus reflecting vagal function, and LF power is related to baroreceptor mechanisms and is related to sympathetic as well as parasympathetic activity. A change from supine to standing posture is associated with higher LF/HF ratios, suggesting a predominant sympathetic activity. Using LF power as an index of sympathetic activity is controversial (Malliani et al. 1991; Cacioppo et al. 1994).

Twenty-four hour records of ECG can give information about the frequencies in the VLF (very low frequency: 0.0033–0.04 Hz) and ULF (ultra low frequency: <0.0033 Hz) ranges. Decreased total and ULF power is associated with sudden death and significant cardiac mortality in cardiac patients and thus is a valuable noninvasive indicator of significant cardiac events (Kleiger et al. 1987; Malik and Camm 1990; Bigger et al. 1992). Though the procedure of frequency domain analyses of HR or HP time series is quite complex, there are several automated programs that routinely report values of these indices along with a standard Holter ECG report. With the automated algorithms and the development of newer software, a clinician can hopefully use these as simple bedside measures. Very low values of HR variability should prompt the clinician to do a thorough cardiological review and also obtain other measures such as QT variability, which are yet research tools but may prove very valuable additions. We have found in several studies that patients with anxiety have decreased HR variability which is pronounced in the ULF power especially during sleep (Yeragani et al. 1990a, 1993; Yeragani 1998). We also found a relatively increased sympathetic function in these patients in standing posture as well as during sleep. Our other studies

show that patients with anxiety have higher increases in relative LF power after oral yohimbine and higher LF/HF ratios after intravenous sodium lactate and isoproterenol compared to normal controls, suggesting a relative increase in cardiac sympathetic function in these patients (Yeragani et al. 1994b, 1995). Recently, we also found that patients with depression have decreased HP variability in 24-hour Holter records (Yeragani 2000).

These findings are important due to the connection between decreased HR variability and significant cardiac mortality, including sudden cardiac death. Several studies also suggest a connection between significant cardiovascular events, anxiety, and depression (Coryell et al. 1986; Weissmann et al. 1990; Kawachi et al. 1994; Musselman et al. 1998). Though these studies are primarily done in adult populations, it still would be worthwhile to use extra caution in treating children with anxiety and depression with drugs that may enhance sympathetic function. In these cases, a baseline ECG and, where possible, monitoring of HR variability may also be of value. If there is a significant drop in HF power of HP and a prolongation of QRS or QTc intervals, it is better to treat the subject with a different medication. In selected patients, a 24-hour ECG would yield valuable information about any cardiac conduction defects or arrhythmias.

QT DISPERSION

Recently, QT dispersion has been used as a research and clinical tool to predict life-threatening arrhythmias (Perkiomaki et al. 1995). In simple terms, QT dispersion is the difference between the longest and the shortest QT interval measured on the 12 lead ECG. These studies have reported greater dispersion of QT in patients who suffered sudden arrhythmic death than in a comparable group without arrhythmias in hypertrophic cardiomyopathy, long QT syndrome, and in patients with chronic heart failure (Linker et al. 1992; Buja et al. 1993; Barr et al. 1994). Malignant arrhythmias are associated with increased heterogeneity of ventricular repolarization. This may also be reflected in QT prolongation. However, QT prolongation may coexist without increased dispersion of ventricular repolarization. If ventricular repolarization is equally prolonged in all regions of the myocardium, a prolonged QT interval can occur with normal QT dispersion. On the other hand, an increased QT dispersion may occur on the background of a normal QT interval. Although QT dispersion has been shown to be more sensitive than the QTc in predicting serious arrhythmias, all these factors should be kept in mind.

However, there is a circadian change in QT and the QTc interval. Hence it is possible that QT dispersion also varies during the day and night. In fact, one recent report has shown that QT dispersion has a clear circadian variation in normal controls, whereas this variation is blunted in patients suffering sudden cardiac death (Molnar et al. 1997).

QT VARIABILITY

The QT interval on the standard ECG reflects ventricular repolarization as described above, and lengthening of QT interval has been related to serious ventricular arrhythmias (Jervell and Lange-Nelson 1957; Binah and Rosen 1992; Tomaselli et al. 1994). In a recent report, Berger and coworkers described an algorithm to calculate QT intervals automatically from the digitized ECG and showed that the QTvi, an index of QT variability, normalized for mean QT over HR variability, normalized for mean HR, was higher in symptomatic patients with dilated cardiomyopathy (Berger et al. 1997). Atiga et al. reported that QTvi was a better predictor of sudden cardiac death in cardiac patients compared to other measures such as ejection fraction, HR variability, and T-wave alternans (Atiga et al. 1998). They also showed that cardiomyopathy associated with beta-chain gene mutation is associated with significantly higher QTvi values (Atiga et al. 2000). Thus, QTvi may be an important noninvasive tool to study certain populations at risk for cardiac mortality. Although generally QT variability follows HR variability, there is not a complete coherence between these two time series.

We have recently shown that isoproterenol and a change from supine to standing posture produce a highly significant increase in QTvi, thus linking it to an increase in sympathetic activity (Yeragani et al. 2000b). We have also found that patients with panic disorder and depression have significantly increased QTvi compared to normal controls, which may be one of the factors responsible for the higher incidence of cardiovascular mortality in these patients (Yeragani et al. 2000c). In another study we found that nortriptyline, a TCA, significantly increased QTvi in patients with panic disorder compared to paroxetine, an SSRI, which had no significant effect on QTvi (Yeragani et al. 2000d). Both drugs were effective for the treatment of anxiety in these patients. Thus, choosing a drug with a safer cardiovascular profile is an important factor. Of particular importance is our recent report suggesting a higher QTvi in children with anxiety disorders compared to normal children, though it was not accompanied by a decreased HR variability (Yeragani et al. 2001). There is also evidence to suggest that the LF power of QT increases during mental stress linking it to a higher sympathetic activity (Dinca-Panaitescu et al. 1999).

We have also shown that the coherence between HR and QT is significantly higher in children compared to adults (Yeragani et al. 2000a), and it should be noted that Berger and coworkers have shown that there is a significantly decreased coherence between these signals in symptomatic patients with dilated cardiomyopathy (Berger et al. 1997). Thus, it may be important not to use a drug that also results in decreased coherence between HR and QT in children, particularly with higher QT variability. Though this measure is still experimental, it may prove valuable in the evaluation of cardiac side effects of a drug or in

choosing a drug with an appropriate pharmacological profile in a given group of patients.

SUDDEN DEATH AND PSYCHOTROPICS IN CHILDREN

In the past few years at least seven deaths have been reported in children who were receiving tricyclic antidepressants (Abramowicz 1990; Riddle et al. 1991, 1993; Varley and McClellan 1997). Most of these children were receiving desipramine, a TCA with mainly noradrenergic activity. Four of these deaths were associated with exercise. Exercise increases cardiac sympathetic activity and may have had a causal role in precipitating fulminant arrhythmias. In children treated with desipramine, ECG and echocardiograms showed higher rates of single or paired premature atrial contractions and runs of supraventricular tachycardia, but there was no evidence of serious arrhythmias that could be potentially lethal.

Tricyclics and some SSRIs such as paroxetine have antimuscarinic effects, and chronic treatment with these agents in higher doses may lead to decreased cardiac vagal function. A relative increase in cardiac sympathetic function, especially during exercise in the presence of other cardiac abnormalities such as prolonged QT interval or higher QT variability, may result in potentially serious arrhythmias. The significant decrease in cardiac vagal function during tricyclic treatment is of particular relevance as a decrease in HR variability is associated with sudden cardiac death (Malliani et al. 1991). The greater central cholinergic modulation of HR in children compared to adults may explain children's faster HR recovery after exercise (Ohuchi et al. 2000). However, any drug that decreases cardiac vagal function may thus have deleterious effects on the myocardium, as one recent report suggested that a delayed recovery of HR during the first minute after graded exercise was a strong predictor of cardiac mortality (Cole et al. 1999). It should be noted that although children generally have a higher HR, they have a significantly higher cardiac vagal activity as suggested by the increased HF power (Yeragani et al. 1994a, 1997). This should protect them from serious cardiac events. However, there may be a group of children where the sympathovagal balance has been adversely affected.

Much attention has been focused on the possibility of a premorbid cardiac condition in these children, as some such deaths can be associated with a long QT syndrome. Thus, there is a great deal of need to identify the possible predictors of sudden death prior to placing children and adolescents on TCAs and other such medications.

It has also been reported that weight loss can be associated with prolonged QT interval, and this should be kept in mind while treating patients with anorexia nervosa with various antidepressants that may prolong the QT interval (Thwaites and Bose 1992). Beard et al. (1986) have also reported that a combination of

psychiatric illness and the use of major tranquilizers were associated with increased sudden unexpected death in women under the age of 60 years. This report again brings the topic of sudden death in psychiatric patients to the forefront.

DRUGS USED IN CHILDREN AND THEIR SPECIFIC EFFECTS ON THE CARDIOVASCULAR SYSTEM

Psychostimulants

Commonly used drugs in this category include methylphenidate, dextroamphetamine, and pemoline. Cardiovascular side effects are rare with psychostimulants. Cardiac arrhythmias are associated with amphetamine-related deaths, and it is possible that the sympathomimetic effects of these agents may have an adverse effect on myocardium in subjects with preexisting cardiac disease or prolonged QTc (Katsumate et al. 1993; Davis and Swalsell 1994). We have recently found that pemoline is associated with an increase in HR and a decrease in cardiac vagal function (Pohl et al. in press). Amphetamines also have a vagolytic effect (Samonina et al. 1989), and methylphenidate can increase HR and BP, and in selected cases with preexisting cardiovascular pathology this might lead to serious arrhythmias. Alcohol abuse also may contribute to cardiac morbidity in association with amphetamines (Zakhari 1991).

Though drugs like 3,4-methylenedioxyamphetamine (MDA, Eve) and 3,4-methylenedioxymethamphetamine (Ecstasy) are not used in clinical practice, these are increasingly becoming popular as street drugs and can result in sudden cardiac death (Dowling et al. 1987).

Antianxiety and Antidepressive Agents

Benzodiazepines

The majority of patients receiving oral benzodiazepines do not experience any significant cardiovascular symptoms. However, intravenous use of diazepam or midazolam can sometimes result in unifocal ventricular premature beats (Ruelofse and van der Bijl 1994).

Some evidence suggests that the use of benzodiazepines can result in decreased HR variability, a decrease in RSA, resulting in a decrease in HF power (Vogel et al. 1996). However, McLeod and coworkers did not find such an association in generalized anxiety patients treated with alprazolam (McLeod et al. 1992).

Tricyclic Antidepressants

TCAs have profound effects on the cardiovascular system due to their strong autonomic effects and also a quinidine-like effect on cardiac conduction (Glass-

man and Bigger 1981). This can lead to negative inotropy, delayed intraventricular conduction, and a prolonged QT interval. These effects can also be dose dependent with different TCAs (Kragh-Sorensen et al. 1973; Georgotas et al. 1987). Clinical doses of TCAs are associated with an increase in supine and standing HR and a small but significant increase in BP (Yeragani et al. 1990b; McLeod et al. 1992). We have shown that imipramine treatment is associated with a significant decrease in HR variability, probably due to its strong anticholinergic effects (Yeragani et al. 1992). In a recent study comparing the effects of nortriptyline and paroxetine, we found that both were associated with decreased HF power, likely due to the antimuscarinic effects of these agents (Yeragani 2000). However, nortriptyline was associated with an increased QT_{vi} while paroxetine was not. This is an important issue due to the recent literature suggesting an association between higher QT_{vi} and sudden cardiac death and coronary artery disease (Atiga et al. 1998, 2000; Vrtovec et al. 2000). It is also relevant here that we recently found higher QT_{vi} in children with anxiety, similar to the findings in the adult group (Yeragani et al. 2001), which should be kept in mind when treating anxious children with antidepressants.

Almost all TCAs are associated with similar ECG changes in prolonging PR, QRS, and QT_c intervals depending on the dosage (Leonard et al. 1995). Biederman et al. (1993) reported no significant cardiac changes associated with 24-hour ECG in children and adolescents treated with desipramine, but later his group concluded that desipramine is an unacceptable choice in children due to the issue of sudden cardiac death (Werry et al. 1995). Wilens and coworkers also found only mild ECG changes in children and adolescents treated with nortriptyline with few age-specific differences (Wilens et al. 1993). Walsh and coworkers (1994) and Mezzacappa et al. (1998) also found a decrease in vagal function after antidepressant treatment in children.

The development of seizures and arrhythmias with TCA overdose is strongly correlated with a QRS interval of >100 msec on routine ECG (Boehnert and Lovejoy 1985). One report also suggests that once the QRS interval is less than 100 msec, the patients may not develop any life-threatening arrhythmias (Shannon 1992). Thus, monitoring ECG is of immense value in cases of TCA poisoning.

Selective Serotonin Reuptake Inhibitors

Drugs such as fluoxetine, paroxetine, and sertraline are not associated with any significant changes in mean HR or BP. One recent report suggests that paroxetine increases cardiac parasympathetic function in patients with panic disorder (Tucker et al. 1997). However, we have found that paroxetine is associated with a significant decrease of HF power of HR in patients with panic disorder, and this is most likely due to its anticholinergic effects (Yeragani et al. 1999). In a study using normal controls, we did not find such a decrease in HF power with

fluoxetine (Pohl and Yeragani et al. in press). We also did not find a significant change in QT_{vi} after paroxetine administration in patients with panic disorder (Yeragani et al. 2000d) compared to nortriptyline, which decreased QT_{vi} significantly. It will be important to comprehensively evaluate the effects of newer SSRIs on these noninvasive measures so that these drugs can be appropriately chosen especially in treating patients with cardiac disease.

Fluoxetine can inhibit cardiac calcium and sodium channels and may have antiarrhythmic as well as proarrhythmic properties due to impairment of atrioventricular or intraventricular conduction and shortening of repolarization (Pacher et al. 2000). This underscores the importance of regular monitoring of ECG, especially in patients with cardiac disease who are on this medication.

Monoamine Oxidase Inhibitors

MAOIs are no longer commonly used due to the advent of newer medications as well as the rare but serious interaction of these drugs with tyramine-containing foods, which results in a hypertensive crisis (Blackwell 1963; Blackwell and Mabbitt 1965). It is interesting to note that in one study of patients with major depression, phenelzine was associated with a significant decrease of the QT_c interval (Georgotas et al. 1987). Postural hypotension is another side effect that occurs commonly in elderly subjects treated with MAOIs.

Other Antidepressants

Trazodone is usually safe and occasionally can result in postural hypotension (Gershon et al. 1986). However, it can produce some toxic effects in people with preexisting cardiac illness (Pohl et al. 1986). Mianserin is usually devoid of cardiac side effects, but maprotiline can result in a decreased QT_c, possibly due to its effects on intracardiac conduction (Edwards and Goldie 1983). Many other antidepressants are now available, and the clinician should carefully evaluate the pharmacological profiles of these agents before using them in children or in patients with cardiac disease. All of these newer agents should be evaluated using some of the more recent techniques described above.

Antipsychotics

Low-potency antipsychotics can cause a small increase in HR, which is rarely of clinical significance. Drugs like chlorpromazine and thioridazine can cause postural hypotension in some patients, especially when the dosage is increased rapidly. Parenteral antipsychotics can result in prolongation of the QT interval (Metzger and Friedman 1993) and may result in torsades de pointes (Hunt and Stern 1995). It is also important to note that hypokalemia may be associated with acute schizophrenia (Hatta et al. 1998), and hypokalemia can also prolong the QT interval (Compton et al. 1996).

There are several reports of sudden death in patients treated with antipsychotic medication (Tsuang et al. 1980; Simpson and Tsuang 1996), some of which conclude that there is a higher incidence of cardiovascular mortality in patients treated with antipsychotics (Newman and Bland 1991). The issue of prolonged QTc may be relevant here. Recently, quetiapine, a novel neuroleptic, reportedly was associated with QT prolongation and sudden death, though it was reported to be safe in another report (Gajwani et al. 2000). Ziprasidone is also under scrutiny for the same reason (Markowitz et al. 1999; Brown et al. 1999). Some of the neuroleptics have a quinidine-like effect, resulting in prolonged QT interval (Warner et al. 1996).

It has been reported that risperidone is safe in the elderly (Madhusoodanan et al. 1999). However, in a feline study, haloperidol, risperidone, sertindole, clozapine, and olanzapine all prolonged QT interval in a concentration-dependent manner (Drici et al. 1998). In one case of risperidone poisoning, QRS was 160 msec and QTc 480 msec, despite some reports suggesting no significant effects on ECG (Ravin and Levenson 1997). Thus, it appears that many of the antipsychotics can prolong QTc, especially in vulnerable subjects.

Several reports suggest that drugs such as chlorpromazine, thioridazine, haloperidol, and pimozide can all result in cardiac arrhythmias, T-wave changes, and TDP (Welch and Chue 2000).

Mood-Stabilizing Agents

Lithium

Lithium can sometimes cause symptomatic sinus node bradyarrhythmias (Rosenqvist et al. 1993). Tilkian and coworkers reported an impairment of chronotropic response to exercise in patients treated with lithium. However, they did not find any sinus node dysfunction during 24-hour ECG recording (Tilkian et al. 1976). Hagman et al. reported no signs of sinus node dysfunction, but this study used only a 12-lead ECG, which may not be sensitive enough to detect these abnormalities (Hagman et al. 1979). Rosenqvist et al. found that sinus node dysfunction was significantly more common in patients treated with lithium (Rosenqvist et al. 1993). They concluded that this effect seemed to be intrinsic and not due to increased parasympathetic tone. During the night the lowest HR was 33 and during the day 37 beats/min; the maximum sinus pause was 1.7 sec and 2.1 sec, respectively. Animal studies suggest that lithium depresses the intracellular potassium concentration and replaces intracellular calcium (El Mallakh 1990). This can cause a decreased depolarization rate and reduced electrical conduction. Lithium-associated hypercalcemia can result in conduction defects (Wolfe et al. 2000). Another factor is lithium-associated hypothyroidism, which can result in sinus node dysfunction (Numata et al. 1999). Lithium can also cause T-wave abnormalities and QTc interval prolongation (Reilly et al. 2000).

Lithium can also result in sudden death in patients with preexisting cardiac problems.

Sodium Valproate

It has been reported that rapid IV use of sodium valproate is safe and causes no ECG abnormalities (Grunze et al. 1999). However, one important issue is valproate-associated carnitine deficiency because of increased renal clearance (Igarashi et al. 1990). Several studies suggest that L-carnitine plays a major role in fatty acid metabolism and helps removal of compounds that are toxic to metabolic pathways (Pepine 1991). Carnitine deficiency can result in cardiomyopathies, and its administration can reverse this process. Carnitine may also have a protective effect in acute as well as chronic ischemic conditions and other conditions such as peripheral vascular disease, congestive cardiac failure, and cardiac arrhythmias. It also prevents cardiotoxicity that results from various toxic agents such as erucic acid, adriamycin, and doxorubicin (De Leonardi et al. 1985; Pasini et al. 1992; Sayed Ahmed et al. 2000). Thus, this is an important issue to be considered during chronic treatment with valproate.

Carbamazepine

Carbamazepine can cause conduction disturbances such as sinus bradycardia and atrioventricular block (Beerman and Edhag 1978; Kasarkis et al. 1992). In dogs it prolongs atrioventricular conduction and decreases ventricular automaticity (Steiner et al. 1970). This can be an issue especially in patients with a preexisting AV block. On the other hand, in one report on 92 young patients receiving carbamazepine, there was no evidence of any sinoatrial or atrioventricular conduction abnormalities on routine ECG (Puletti et al. 1991). It appears that the elderly and people with pre existing cardiac problems are the most vulnerable.

Other Drugs Used in Children with Psychiatric Disorders

Clonidine

Clonidine is an α_2 -adrenergic agonist, which decreases BP and is occasionally used as an antihypertensive. However, in psychiatry it is sometimes used to treat Tourette's syndrome and also attention deficit disorder. Thus, it is important to have some understanding of the basic effects of clonidine on heart and vessels. Incidentally clonidine was also tried as an anxiolytic. In a recent study on 42 children treated with clonidine for different disorders, Kofoed and coworkers did not find any significant cardiovascular side effects (Kofoed et al. 1999). The main side effect of clonidine is thus hypotension and bradycardia, especially in high doses. However, suddenly stopping the drug can also lead to a rebound hypertension with serious consequences. Clonidine can induce bradycardia and irregular firing of the sinoatrial node (Dowson et al. 1989). With the increasing use of

clonidine patches, especially in the pediatric population, one should be aware of the possibility of bradycardia, severe hypotension, and other cardiac dysrhythmias (Harris 1990). A special point to keep in mind is that the combination of clonidine with beta-blockers such as propranolol may lead to serious bradyarrhythmias.

Calcium Channel Blockers

Calcium channel blockers such as nifedipine and verapamil have been sometimes used as an experimental strategy in patients with affective disorders who do not respond to other drugs. The common side effects are tachycardia, postural hypotension, and headaches. There is some doubt as to whether the use of these agents is associated with sudden cardiac death. In fact, verapamil can decrease rapid ventricular rate in chronic atrial fibrillation, and the sublingual route can be effective in this regard (Incze et al. 1998). Thus, the effects of these agents should be evaluated on a case-by-case basis.

SPECIAL RISKS OF DRUG INTERACTIONS

A detailed description of all drug-drug interactions are dealt with in detail in many books and is beyond the scope of this chapter. Pharmacokinetic interactions can result in abnormal absorption, protein binding, drug metabolism, and enzyme induction and inhibition and can affect the cytochrome P450 system and excretion of drugs (Krishnan et al. 1996). Pharmacodynamic effects occur directly on the receptors or through modulation of receptors. A combination of MAOIs and serotonin can result in serotonin syndrome, which could end in death. Tricyclics can interact with sympathomimetic agents and potentiate their effects (Yeragani et al. 1996).

SIMPLE GUIDELINES TO AVOID SERIOUS SIDE EFFECTS

It should always be remembered that children are dependent on adults, and thus the education of parents or guardians is of paramount importance in relation to the side effects of any drug used in a child. It is important in a clinical setting to take a good history of any medical condition in children that seek psychiatric help, whether they will be placed on psychotropic drugs or not. This underscores the importance of having a baseline ECG for later reference. This should certainly include any history of congenital heart disease, episodes of palpitations, breathlessness, and fainting spells. Fatigue and chest pain and breathlessness on exertion, edema of feet, and cyanosis also should be enquired about. During clinical examination, any murmurs or clicks should be looked for. A routine 12-lead ECG is of immense value as one could identify serious problems such as increased QRS or QT duration. In children with an abnormal ECG, calculation of QT dis-

persion and a Holter record would be very useful to identify any runs of tachycardia or other serious arrhythmias in a longer strip of ECG. An echocardiogram would certainly rule out any serious structural abnormalities of the heart. In selected cases it may be a good idea to measure HR and QT variability where possible and facilities exist.

In a child with a relatively higher HR it may be better not to use a TCA, which may further increase HR and prolong QTc, which may be dangerous. Alternate drugs such as SSRIs may be a better choice in such situations. It is also important to educate the child (as much as can be done) as well as the family about some of the potential and serious side effects, including the dangerous effects of overdose. The dosage also should be tailored to the weight of the child; it is always wise to start with lower doses as prolonged QTc is often a dose-dependent phenomenon. In a recent article, Roose and Spatz addressed the issue of which drug to choose in patients with ischemic heart disease while treating depression (Roose and Spatz 1999). This information could serve as a guideline to look at various options in relation to a preexisting illness.

The other important point is to carefully pay attention to drug-drug interactions, as this could potentially be lethal, as described above. This is especially important because many children may be receiving a combination of an antipsychotic, a TCA, and other anticholinergic agents. The addition of an SSRI may seriously affect the concentrations of the other drugs. While it is not practical to list all the drug interactions in this chapter, this factor is always important. The essential point here is to use as few drugs as possible. It should also be noted that there is recent warning from the pharmaceutical company Novartis in regards to thioridazine and QTc prolongation. They have come up with specific guidelines to prescribe this medication after a study showed a dose-related prolongation of the QTc interval with thioridazine (Hartigan-Go et al. 1996). The same caution probably applies to mesoridazine.

It is important that the clinician has a high degree of awareness as to some of the manifestations of postural hypotension, syncope, palpitations, and other relevant symptoms so that changes can be made in the beginning stages of treatment.

MANAGEMENT

If there is an adverse effect during treatment, the type of the side effect and any factors that triggered the event, especially polypharmacy, should be kept in mind, and depending on the nature and severity of the adverse effect, the dosage should be decreased or the drug should be stopped and substituted with another one. In case of serious side effects that require intensive care to maintain respiration and circulation, the treating clinicians should have all the details that led to such an adverse effect before any specific treatment is undertaken.

SUMMARY

This chapter is intended to give a brief description of various cardiac side effects that can result from psychotropic usage with a special emphasis on some lethal consequences. The focus is also on some of the latest measures, which are as yet research tools that might help the clinician to screen patients who may develop potentially serious cardiac effects while receiving some of these drugs. With the advent of several new antipsychotics and antidepressants, it is easier to replace an offending agent with a drug that has a different side effect profile. Here it is important to have some insight into the neurochemical and neurophysiological effects of these drugs as this could predict the side effect profile. The other important point is the development of noninvasive indices such as HRV, QT_{vi}, and QT dispersion to understand and predict sudden cardiac death. It appears that in the setting of decreased HR variability, higher QT dispersion and higher QT variability, and poor coherence between QT and HR variability in association with a prolonged QT_c, there is a definite risk for the patient to develop fulminant arrhythmias. This underscores the importance of developing new drugs and other techniques that result in decreases in QT_{vi} and QT dispersion and shorten QT_c in different treatment settings.

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7

Psychostimulants

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The psychostimulants methylphenidate (Ritalin, Methylin, Metadate ER, Concerta), dextroamphetamine (Dexedrine), dextro (d) and levo (l) amphetamine (Adderall), and magnesium pemoline (Cylert) remain the most commonly prescribed medications in child and adolescent psychiatry, despite their having been approved by the U.S. Food and Drug Administration (FDA) only for attention-deficit hyperactivity disorder (ADHD) in children and adolescents and for narcolepsy in adults (Barkley, 1990; Dulcan, 1990; Gillberg et al., 1997; Findling and Dogin, 1998; PDR, 1999; Greenhill et al., 1999; NIH Consensus Statement on ADHD, 2000). ADHD, the most common neuropsychiatric disorder of childhood, affects approximately 3–5% of the school-age population (NIH Consensus Statement on ADHD, 2000). In recent years there has been a marked increase (2.5-fold) in school-age children, 5–14 years old, receiving psychostimulants, predominantly methylphenidate for ADHD symptoms (Safer et al., 1996). Part of this increase may be reflected by public health initiatives focused on identification and inclusion of more female patients, treatment of more high school-age students, and longer duration of treatment (Safer et al., 1996). Nearly 3% of children 5–18 years old in the United States received psychostimulant medication by 1995 (Goldman et al., 1998). An especially dramatic increase in psychostimulant pre-

scriptions (2- to 3-fold), primarily methylphenidate (Ritalin), was also recently reported in preschool-age children 2–4 years old enrolled in Midwestern and mid-Atlantic Medicaid programs and a health maintenance organization in the Northwest (Zito et al., 2000). Nearly 60% of 223 Michigan Medicaid patients under 4 years of age received at least one medication, most commonly methylphenidate, to treat ADHD in 1995–1996 (Rappley et al., 1998).

While the largest increase in methylphenidate prescriptions has been reported in teenagers 15–19 years old (311%), striking increases were also observed in school-age children 5–14 years old (176%) and in preschool children 2–4 years old (169%) (Zito et al., 2000). Only a small number of randomized controlled trials of stimulants have been reported in preschool-age children that demonstrated their efficacy in this population (Spencer et al., 1996a; Handen et al., 1999). Preschool children also appear to be more sensitive to stimulant side effects, in some but not all studies, than older children (Firestone et al., 1998; Conners, 1975; Barkeley, 1988a, 1988b). The Physician's Desk Reference (PDR) (2001) specifically advises against prescribing methylphenidate in children under 6 years of age (only amphetamine compounds have FDA approval for children 3 years of age and older). Nonetheless, physicians are frequently prescribing this medication off-label in preschool-age children.

The aforementioned recently reported data have resulted in the psychostimulants remaining controversial because of fears about their potential for abuse and addiction, which led certain special interest groups to lobby for their immediate recall and removal from the market. In fact, methylphenidate and amphetamine compounds (Dexedrine and Adderall) are classified by the FDA as Schedule II drugs, the most restrictive classification for drugs considered to be medically useful (PDR, 2001). Magnesium pemoline (Cylert) is classified as a Schedule IV drug and is considered to have a lower potential for abuse than the other stimulants (PDR, 2001). Nonetheless, the authors wish to emphasize that in the field of child psychiatry, and in psychiatry in general, the use of stimulant medications, particularly methylphenidate and amphetamine compounds, is not considered controversial. These medications are solid, first-line, bread-and-butter type medications with a remarkably benign side effect profile. The disorder that they are most commonly used to treat, ADHD, is one with marked functional impairment, long-term morbidity, and enormous consequences for the child and family. There are over 160 randomized controlled trials demonstrating the short-term efficacy of psychostimulants for ADHD (Spencer et al., 1996a; Greenhill et al., 1999). Approximately 70% of children improve on psychostimulant medications. Recent long-term studies have demonstrated that stimulants have continued efficacy and safety in studies between 15 and 24 months (Gillberg et al., 1997; Greenhill et al., 1999; MTA Cooperative Group, 1999a; 1999b; NIH Consensus Statement on ADHD, 2000). Longer-term studies are currently ongoing. In addition, a recent multicenter investigation found stimulant medication with

appropriate dosage titration and close monitoring for a period of 1 year to be superior to state-of-the-art behavioral therapy in treating ADHD (NIH Consensus Statement on ADHD, 2000). Specifically, medication was significantly more efficacious in reducing distractibility/reduced attention span, hyperactivity, impulsivity, and aggression than behavioral therapy. It should be noted, however, that parents and teachers reported greater improvement in social skills, reading ability, and anxiety levels with combination therapy than with medication alone. Children treated in the study with regular and intense medication monitoring and careful dosage titration only and children treated with both this medication regimen and behavioral therapy had a greater reduction in ADHD symptomatology than did children who received standard community care, which not uncommonly involved treatment with stimulant medications and/or other psychosocial approaches (NIH Consensus Statement on ADHD, 2000). This aforementioned investigation also did not investigate whether concomitant behavioral therapy might help reduce medication needs or potentially help target refractory behaviors necessitating medication intervention (NIH Consensus Statement on ADHD, 2000). It should be noted, however, that ADHD children with comorbid anxiety disorder responded particularly well to behavioral interventions (MTA Cooperative Group, 1999b).

Although more long-term studies are needed, stimulants have demonstrated efficacy with favorable side effect profiles (see below). Moreover, children and adolescents with ADHD exhibit a two- to fourfold increased risk for substance abuse, and current data show no evidence that the use of stimulant medication at standard prescribed dosages results in increased use, or abuse of, and dependence on, recreational or prescription drugs, or in dependence on and addiction to the stimulants themselves (Gadow, 1981; Barkley, 1990; Dulcan, 1990). Close monitoring of the child or adolescent and his or her family members for the potential for abuse are required when stimulants are prescribed. When used properly, the stimulants are beneficial and safe, as well as cost-effective, in decreasing hyperactivity, distractibility, impulsivity, and fidgetiness, and in increasing attention span. State-dependent learning is also not a problem when stimulants are used (Barkley, 1990). Cognitive effects may respond optimally to relatively modest doses of stimulant medications, while behavioral symptoms may require larger doses (Pelham, 1986; Pelham and Hoza, 1987; Pelham, 1989; Gillberg et al., 1997; Pelham, 1986; Findling and Dogin, 1998; Greenhill et al., 1999; NIH Consensus Statement on ADHD, 2000). No normative clinical or laboratory values have been elucidated at this time.

Carlson and associates (1993) compared the effects of methylphenidate with those of placebo on the performance of ADHD boys after their success or failure at tasks assigned them. They provided evidence for a "salutatory" effect of methylphenidate on the boys' performance and perceptions after attempting to solve both solvable and unsolvable puzzles. Boys exposed to unsolvable puzzles

demonstrated increased persistence on a subsequent generalization task when receiving methylphenidate as compared with placebo. Five measures of phonologic processing, including the Posner letter-matching test, were used in an attempt to isolate the effects of methylphenidate to parameter estimates of selective attention, the basic cognitive process of retrieving name codes from permanent memory, and a constant term that represented nonspecific aspects of information processing. Responses to the letter-matching stimuli were found to be more rapid with methylphenidate than with placebo (Balthazor et al., 1991). It is important to note that improvement in performance was isolated to the parameter estimate that reflected nonspecific aspects of information processing.

A lack of active medication effect was found on the other measures of phonologic processing, supporting the Posner task finding suggesting that methylphenidate exerts beneficial effects on academic processing through general rather than specific aspects of information processing (Balthazor et al., 1991). More recently, Swanson et al. (1998) reported that compared to placebo, Adderall treatment resulted in improvement in objective measures of behavior including mathematics problems attempted and mathematic problems completed correctly.

CHEMICAL PROPERTIES

For the chemical properties of the psychostimulants, see Table 1 and Figures 1–3.

The stimulants used in child and adolescent psychiatry are sympathomimetic amines that may be administered orally (Barkley, 1990; Dulcan, 1990; Arana and Hyman, 1991; PDR, 2001). They then cross from the blood-brain barrier. The onset of action for methylphenidate and amphetamine compounds is generally observed within 20 minutes to one hour, with a 3- to 6-hour duration of action. Duration of action for stimulants appears to be dose-related (Swanson et al., 1998). Stimulants of the central nervous system (CNS) exert their maximum effect when they are being most rapidly absorbed, and clinical efficacy is probably related to the rate of rise of the blood level (Dulcan, 1990). This is when the target symptoms, including hyperactivity, distractibility, inattentiveness, impulsivity, and fidgetiness, are most susceptible to the stimulants' effects. The clinical effectiveness of the stimulants has not been shown to correlate with absolute or peak blood levels (Dulcan, 1990), and no therapeutic window has as yet been delineated for any of them (Barkley, 1990; Dulcan, 1990). Sustained-release preparations of methylphenidate may have their onset of action delayed as long as 3 hours, with a shorter duration of action and more day-to-day variability than two doses of regular methylphenidate given around breakfast and lunchtime (Pelham et al., 1987, 1990).

Pelham and associates (1987) compared the relative efficacy of standard methylphenidate, sustained-release methylphenidate, sustained release dextroamphetamine, and pemoline in a double-blind, placebo-controlled crossover evalua-

TABLE 1 Pharmacokinetics of CNS Stimulants in Children and Adolescents

Generic name (brand name)	Onset of action	Peak plasma concentration (hr)	Plasma half-life (hr)	Metabolism and excretion	Comments
Methylphenidate (Ritalin, Methylin, Metadate)	30–60 min, up to 3 hr for SR and ER	1–2, 4–5 for SR and ER	1–2	Metabolized by hepatic microsomal enzymes	Drug concentrations higher in brain than in blood
Dextroamphetamine sul- fate (dextro and levo amphetamine Adderal)	30–60 min, 1– 2 hr for span- sule	2, 8–10 for spansule	6–8	Metabolized partly by liver and partly ex- creted unchanged in urine	Excretion increased by acidi- fication of urine, decreased by alkalization; develops high concentration in brain
Magnesium pemoline (Cylert)	Variable, acute, and delayed ef- fects	2–4	8–12	Metabolized 60% by the liver and excreted 40% unchanged in urine	Without significant sympatho- mimetic activity, half-life increased with chronic ad- ministration

SR, Sustained release; ER, extended release.

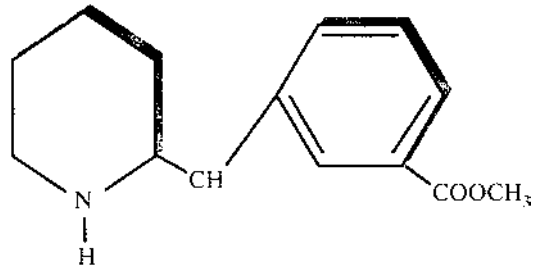


FIGURE 1 Molecular structure of methylphenidate.

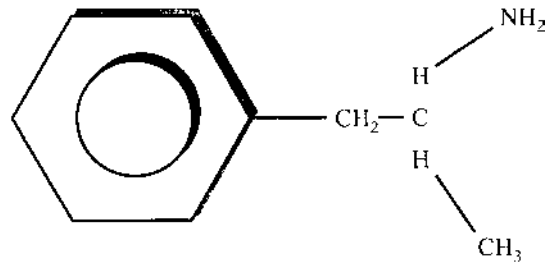


FIGURE 2 Molecular structure of amphetamine.

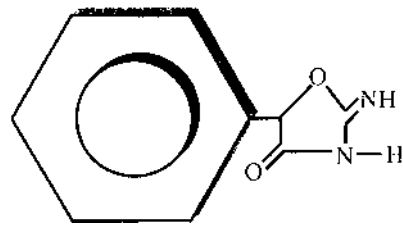


FIGURE 3 Molecular structure of pemoline.

tion of 22 ADHD children. They found that sustained-release dextroamphetamine and pemoline produced the most consistent beneficial effects and were recommended for 10 of the 15 children who were responders to medication. The continuous performance task results demonstrated that all four medications had an effect within 2 hours of ingestion, and the effects lasted for 9 hours (Pelham et al., 1990). Swanson et al. (1998) also demonstrated that over 90% of ADHD patients

treated with Adderall were able to be maintained on once- or twice-daily therapy. Approximately 40% of 611 children 3–12 years of age with ADHD were able to be maintained on once-daily dosing with Adderall, and more than half were effectively maintained on twice-daily dosing. Less than 10% of patients required dosing more than three times per day. Manos et al. (1999) also found that single-dose therapy with Adderall was comparably effective to twice-daily doses of methylphenidate. Adderall contains dextro (d) and levo (l) amphetamine and contains amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine saccharate in equal combinations (Findling and Dogin, 1998). The advantage of sustained-release preparations, when successful, is that they may obviate the need for medication administration during the school period.

INDICATIONS

Indications for use are shown in Table 2.

ADHD in Children and Adolescents

More than 4 million ADHD patients visit outpatient clinics in the United States each year (Swanson et al., 1995). As many as 90% of these patients are being prescribed psychotropic medication (Swanson et al., 1995; Greenhill et al., 1999; Zito et al., 2000). Most (70–90%) of these prescriptions are for the stimulant methylphenidate. Despite concerns expressed by the public, media, and the FDA,

TABLE 2 Indications for CNS Stimulants in Childhood and Adolescent Psychiatry

FDA-approved indications
ADHD in childhood and adolescence
Narcolepsy (methylphenidate, dextroamphetamine and Adderall)
Exogenous obesity (dextroamphetamine)
Possible indications
ADHD in preschool children
Undifferentiated attention-deficit disorder
ADHD in children with conduct disturbances
ADHD in children with developmental disabilities
ADHD symptoms in children and adolescents with fragile X syndrome
ADHD symptoms in children and adolescents with head trauma and/or organic brain disease
ADHD in children and/or adolescents with tic disorders (i.e., Tourette's syndrome)
Potentiation of narcotic analgesia

the increase does not appear to be due to factors such as abuse or financial incentive (Goldman et al., 1998). In fact, Jensen et al. (1999) studied four different communities in the United States and found that only one eighth of ADHD children were receiving medication treatment. Their data did not demonstrate that stimulants were being overprescribed. They advocated educational programs for parents, physicians, and mental health care professionals focused on effective treatment for ADHD. While recent investigation suggests that stimulant and other psychotropic medications may be overprescribed, particularly in preschool-age children (Zito et al., 2000), it also appears that many children who could benefit from intense, standardized administration of these medications are not being treated. The key is precision of diagnosis, which results in optimal treatment. Rigorous diagnostic assessment of ADHD is clearly warranted. In contrast, prescribing stimulant medication based on a child's being "hyper" on a single outpatient office visit and without adequate evaluation is obviously contraindicated.

ADHD has been most often considered a disorder of catecholamine underactivity with dysregulation in dopaminergic and noradrenergic systems (Zametkin and Rapoport, 1987; Arnsten et al., 1996; Pliszka et al., 1996; Solanto, 1998; Biederman and Spencer, 1999). Volkow et al. (1995, 1998, 2001) demonstrated that the stimulants, particularly oral methylphenidate, bind to the dopamine transporter and yield a 20% increase in synaptic dopamine. Seeman and Madras (1998) have reported a 60-fold increase in extracellular dopamine concentrations during normal nerve activity. Methylphenidate and dextroamphetamine decrease locomotion in both humans and animals, while at high doses they actually stimulate motor activity (Figs. 4 and 5). Specifically, the stimulants bind to the dopamine transporter on presynaptic axons, blocking reuptake, thus leading to an increase in synaptic dopamine (Volkow et al., 2001). Elevated extracellular dopamine eventually leads to a decrease in dopamine receptors on postsynaptic neurons. However, the stimulant-related reduction in psychomotor activity has been thought to be mediated by dopamine stimulation of striatal structures and secondary effects on prefrontal areas (Volkow et al., 2001). Increased extracellular dopamine concentrations decrease the number of D1 and D2 dopamine receptors. Conversely, high-dose methylphenidate and dextroamphetamine administration result in stimulation of the nervous system.

Until recently, stimulant medications were predominantly prescribed to children 6–10 years of age and generally were discontinued around the onset of puberty and adolescence. Many practicing clinicians believed that ADHD remitted at puberty, but further investigation has demonstrated that its course is extremely variable and the symptoms can and do persist into adolescence and adulthood (Wender, 1987; Barkley et al., 1991a; Spencer et al., 1996a). Stimulants have been found to be effective in treating ADHD symptoms throughout life (Wender, 1987; Pelham et al., 1991; Evans and Pelham, 1991; Spencer et al., 1996a), which has led to a dramatic increase in their use for adolescents, preado-

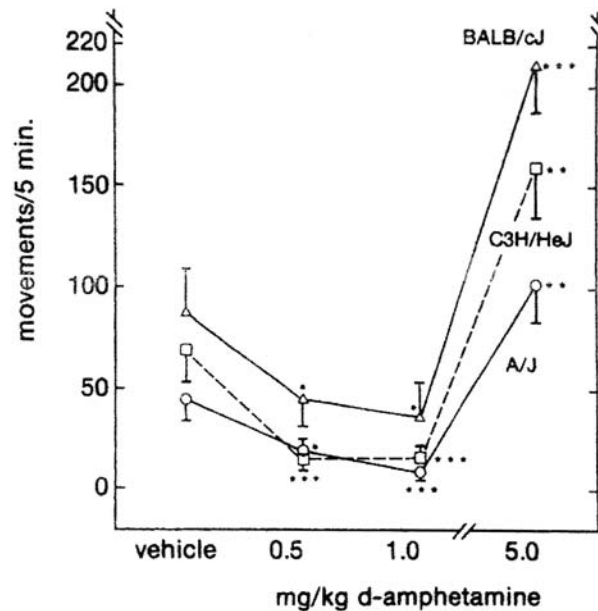


FIGURE 4 Biphasic action of dextroamphetamine (d-amphetamine) on mice, eliciting hypolocomotion at low doses (i.p.), but stimulating motor activity at high doses. The spontaneous motor activity was measured using Stoelting sensor activity meters. The different strains of mice, BALB/cJ, C3H/He, and A/J, were obtained from Jackson Laboratories (Bar Harbor, ME). The asterisks indicate locomotor activity statistically significantly different from control ($p < 0.02$). (From Seeman and Madras, 1998.)

lescents, preschoolers, and adults (Spencer et al., 1996a; Zito et al., 2000). Nonetheless, while many persons with ADHD have been treated with stimulant medications, these drugs are often not prescribed correctly.

Case History

A 10-year-old boy was referred for child psychiatric evaluation because of “problem school behavior.” He was found to have a history of disruptive behavior since the age of 2 and, according to his mother, had since become more “hyper.” She and her husband had hoped that the child would “grow out of it,” but instead his behavior deteriorated. He was failing all of his fifth-grade courses, despite school psychoeducational assessment that revealed that he functioned in the above-average range. The school was threatening to expel him for his disruptive

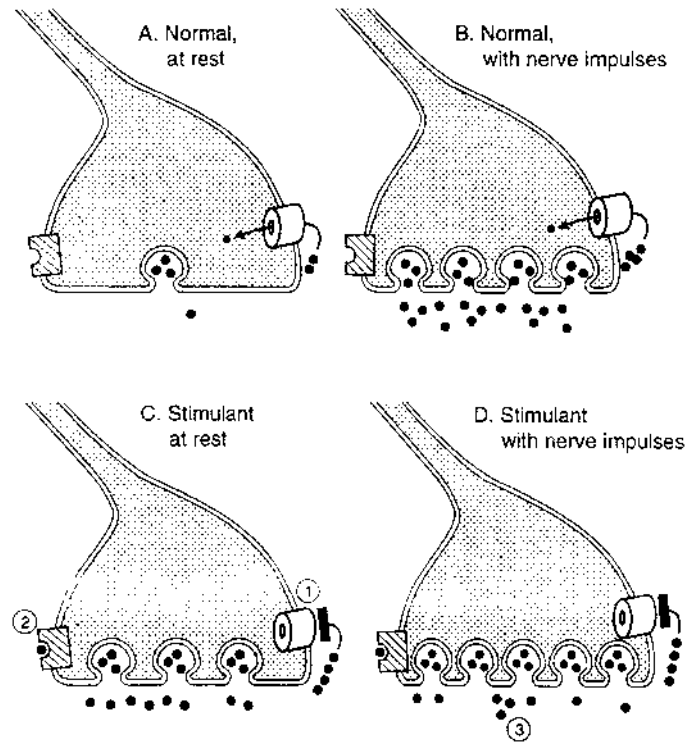


FIGURE 5 Cell pharmacology of stimulant drug action. (A) Normal resting level of extracellular dopamine is of the order of 4 nM. (B) The transient rise of extracellular dopamine during a normal nerve impulse returns to normal levels by diffusion and by reuptake via the dopamine transporter. (C) In the presence of locomotor-inhibiting doses of methylphenidate or dextroamphetamine, the dopamine transporter is blocked (step 1) and the resting extracellular level of dopamine rises about sixfold. (D) The elevated resting level of dopamine acts on presynaptic dopamine D2 receptors on the nerve terminal (step 2), resulting in an impulse-associated release of dopamine (step 3), which is less than the sixfold rise between A and C, and proportionately less than the percent rise from A to B. This lower differential rise in pulsatile dopamine acts on postsynaptic D2 dopamine receptors to result in less locomotor activity. Higher doses of stimulants markedly elevate the resting level of extracellular dopamine and result in marked behavioral stimulation, which is not overcome by the steps shown here. (From Seeman and Madras, 1998.)

behavior, which included an inability to stay seated in the classroom and to wait in line with the other children, high levels of motoric activity, easy distractibility, an inability to attend to tasks, and impulsivity. His parents confirmed similar behavior at home. There was no evidence for mood disorder, psychosis, or drug and alcohol use. The family history was noncontributory.

A comprehensive behavioral management program was implemented. This, however, proved to only be minimally effective. High rates of hyperactivity were still observed as measured by Parent and Teachers Conner's Questionnaires. A methylphenidate trial was initiated. The patient started on a drug A/B trial: methylphenidate versus placebo. Doses of methylphenidate included 5 mg b.i.d., 10 mg b.i.d., 10/15 mg, 15 mg b.i.d., 20/15 mg, 20/20 mg, and placebo. The patient, his family, and his teachers all were blind to the patient's medication status. The parents and teachers were asked to fill out the Conner's Questionnaire forms, and the teachers also filled out a daily report card assessing his behavior during each class period. Only the treating psychiatrist knew the dose of medication the patient was receiving. It was determined that the patient responded best (greatest reduction in target symptoms with fewest side effects) to a dose of methylphenidate 15 mg b.i.d. Combined with the comprehensive behavioral program, he was maintained on this dose of methylphenidate. At 6 months, he continued to show good improvement, was no longer failing all of his classes, and his homeroom teacher described him as "being a different child."

CLINICAL EFFICACY

Hyperactivity

Stimulants significantly reduce hyperactivity in children and adolescents with ADHD (Barkley, 1990; Dulcan, 1990). It should be noted that while increased activity during structured settings such as the classroom is decreased, it has long been held that most children with ADHD are still appropriately active during periods of recreation and play. However, naturalistic actometer data has shown that ADHD children have lower activity levels than children with no mental disorder during playground recess time (Porrino et al., 1985).

Distractibility

The stimulants are also quite effective in decreasing distractibility and increasing attention span. This is particularly evident in structured settings such as the classroom (Stephens et al., 1984; Balthazor et al., 1991; Pelham et al., 1991; Evans and Pelham, 1991).

Social Interactions

Stimulants have been shown to significantly increase a child's responsiveness to and compliance with parental commands (Barkley, 1985). The children also function better interpersonally with both peers and adults, although the stimulants do not normalize social behavior (Whalen et al., 1989). These results are supported by recent multicenter controlled investigations (MTA Cooperative Group, 1999a, 1999b). Combining stimulant with behavioral therapy may further facilitate improvement in social skills (NIH Consensus Statement on ADHD, 2000). Stimulant use has been shown to improve impulsivity, aggression, and noncompliance associated with ADHD (Barkley, 1977, 1990), but not in children who have pure oppositional defiant and conduct disorders without ADHD. However, in children who carry both diagnoses, the aggression and impulsivity may decrease when the ADHD has been effectively treated (Klorman et al., 1988; Hinshaw et al., 1989; Murphy et al., 1992).

Academic Achievement

By decreasing the interfering behaviors associated with ADHD, stimulant use would be expected to result in the enhancement of academic achievement. Nonetheless, up until very recently it was believed that there was only minimal or no improvement in academic performance (Barkley and Cunningham, 1978). Recent investigation, however, has revealed that the use of methylphenidate can significantly improve accuracy and productivity in academic settings (Pelham et al., 1985; Rapport et al., 1986; Douglas et al., 1988). Recent investigation with Adderall has also demonstrated significant dose-related improvement in age-appropriate mathematics problems attempted and completed compared to the placebo condition (Swanson et al., 1998). These studies had the advantage over previous studies and reviews (Barkley and Cunningham, 1978) of utilizing written assignments given by the child's teachers as opposed to standardized achievement tests to measure academic performance. Moreover, Pelham (1986) argued persuasively that stimulants improve accuracy and speed most significantly in those areas that have already been partially learned but require practice in such subjects as math and spelling. It must be emphasized that stimulant-induced learning has not been demonstrated to be state dependent (Aman, 1982; Stephens et al., 1984) so that allowing ADHD children to go on medication-free holidays is not likely to result in either short- or long-term disruption of learning.

Motivation

Motivation may be improved since there are fewer impediments to allow the child to perform required tasks (Dulcan, 1990). This may also facilitate enhancement of academic achievement. This remains an area of active investigation, and the stimulants' exact effects on motivation are unclear. Further study is necessary.

Mood and Emotion

In contrast to adults, children rarely experience mood elevations or euphoric effects when taking stimulants (Rapoport et al., 1980), although they may precipitate a worsening of mood and/or irritability (see Side Effects). Nonetheless, children and adolescents treated with stimulants consistently rate themselves as “happier” compared to when they receive placebo (Carlson et al., 1993). It should be noted that children with ADHD carry an increased risk for developing comorbid major depression (Biederman et al., 1996). Though they have sometimes been used to treat adult depression, stimulants are currently not recommended for treating dysphoria and depression in children. Caution is also necessary in using these medications in patients with bipolar disorder. There has been recent discussion as to whether prepubertal mania is often mistaken for ADHD (Biederman et al., 1998), underscoring the necessity of precision in diagnostic assessment for appropriate treatment intervention. Bipolar disorder and ADHD can also coexist (see Chapter 13).

Clinical Concern

Behavioral interventions such as social skills training, problem-solving skills, behavioral modification, and family therapy should be attempted before initiating a stimulant trial (Barkley, 1990) and may be especially beneficial in combination with medication treatment (NIH Consensus Statement on ADHD, 2000). If behavioral interventions are insufficient or untenable, then stimulant medications can be used to help ameliorate the behavior. While recent long-term study demonstrated stimulant medication to be superior to behavioral therapy as well as little additional benefit for core ADHD symptoms when combination behavioral and medication therapy were employed (NIH Consensus Statement on ADHD, 2000), delineating whether behavioral and environmental interventions can ameliorate problematic behaviors is warranted, particularly in younger children. This may also help better target medication for problematic and refractory symptoms and possibly lower stimulant dose requirements for treatment of ADHD (NIH Consensus Statement on ADHD, 2000). Nonetheless, we currently cannot predict prior to treatment those ADHD patients most likely to respond to a particular stimulant medication (Pelham and Milich, 1991). It should also be noted that there are still no studies in which children treated with stimulants over several years have been studied to determine the long-term effects of these medications as these children progress into adulthood. Thus, we do not know the long-term effects of stimulants on brain development. Dopaminergic and noradrenergic systems continue to mature through adolescence and young adulthood (Goldman-Rakic and Brown, 1982; Rosenberg and Lewis, 1994, 1995). It is important to point out that ADHD significantly impairs all domains of functioning, often resulting in family crises. Moreover, there are increased risks for substance abuse

TABLE 3 Important Considerations When Prescribing Stimulants

Use with caution in children and adolescents with:
Conduct disorders
History of substance abuse/dependence
Antisocial family members
Substance-abusing/dependent family members
Tic disorders (i.e., Tourette's syndrome)
Mood disorder (e.g., bipolar disorder, major depression)
Psychosis
Failure to thrive (i.e., physical retardation)
Liver impairment (especially magnesium pemoline)

and other problematic behaviors. Children who do not receive proper treatment are at a greatly increased risk of having Axis I and II diagnoses (i.e., substance abuse and antisocial personality disorder) (Weiss et al., 1985; Wender, 1987). Therefore, a cost-benefit and risk-benefit analysis is indicated when psychotropic medication is considered. To reiterate, when prescribed appropriately, stimulant medication is extremely effective for reducing core ADHD behaviors and has a remarkably benign side effect profile.

Trials of a medication should be performed to assess whether or not a child truly needs the medication. Methylphenidate and dextroamphetamine sulfate are short-acting and lend themselves well to a placebo versus medication trial (called A/B drug trials) in which the patient serves as his or her own control (Pelham and Milich, 1991). Tables 3–4 indicate important considerations when prescribing stimulants, core ADHD symptoms targeted by stimulant medication, and schema for pharmacological intervention for ADHD.

Narcolepsy

Narcolepsy is a disorder of excessive daytime sleepiness in which the person experiences sudden-onset rapid-eye movement (REM) sleep attacks (Kaplan and Sadock, 1991). Cataplectic attacks consisting of the total or partial collapse of skeletal muscle tone are commonly observed in narcolepsy. It is usually diagnosed in the second decade of life. Polysomnographic studies are required to make a definitive diagnosis, with behavioral and educational interventions generally attempted first (Kaplan and Sadock, 1991). These consist of looking into the sleep habits and hygiene of the patient and family and having the patient avoid irregular sleep schedules. Patients are often advised to take short naps to determine whether these will ameliorate the condition—an approach that can preclude the need for pharmacological intervention. If behavioral and educational methods

TABLE 4 How to Do an Outpatient Medication Assessment

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1. Talk with the child's pediatrician/primary practitioner about the assessment and elicit cooperation. The child should have a recent physical exam to rule out conditions that preclude an assessment with stimulants. Emphasize that the evaluation will provide objective information that can be used in long-term treatment planning and will protect both the child's and the practitioner's best interests.
 2. Select type and doses of medication. Standard protocol utilized in our ADHD clinic includes placebo, 0.3 mg/kg methylphenidate b.i.d., and 0.6 mg/kg methylphenidate b.i.d. (reduced to 0.15 and 0.3 mg/kg for low and high doses, respectively, for overweight children, for older and therefore heavier children, and for children who do not have behavior problems.) Other preparations could be employed for a variety of reasons (e.g., need long-acting preparation because school will not administer midday dose). If using d-amphetamine, halve the dose, and if using pemoline, use six times a single methylphenidate dose with a.m. administration only. Ensure that times of the day during which the child exhibits problems overlap with peak medication times.
 3. Establish a random schedule in which medication condition changes daily, but limit randomization to ensure that each dose is given at least once per week (e.g., week 1: Placebo, 0.3, Placebo, 0.6, 0.3). Have each dose occur between 5 and 10 times or until stable data have been obtained and a pattern or lack thereof is clear.
 4. Have the pharmacist package medication and placebo in identical, self-locking opaque capsules in dated, individual envelopes in random order.
 5. Let everyone, including the child, know that the assessment is occurring, but keep everyone who will provide any information regarding the child's response blind to the conditions.
 6. Have teacher rate child on IOWA Conner's daily (as measure of main effect) and have parent complete Abbreviated Conner's nightly (as measure of rebound), along with a brief side-effects rating scale.
 7. Also gather daily objective information from the school regarding the child's major behavioral and academic problems.
 8. If no. 9 is too difficult for the teacher, use daily report card record (already established for the behavioral intervention) and teacher ratings to assess response.
 9. After the assessment has been completed, break blind and compute means and standards deviations for dependent measures within each condition.
 10. Giving most weight to the child's major problem areas, determine whether or not the incremental improvement obtained with medication outweighs any side effects observed. Consider variability and final level of functioning when assessing response.
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Source: Pelham and Milich, 1991.

are inadequate, particularly if the child falls asleep in school, the CNS stimulants methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) and Adderall can effectively treat the symptoms of these sleep problems (Arana and Hyman, 1991; Kaplan and Sadock, 1991; PDR, 2001). High dosages of both methylphenidate and amphetamine compounds may be required (20–200 mg/day each in divided doses). However, tolerance often develops, making it even more important to encourage the patient to continue to try to take brief naps and to take drug holidays from medications whenever possible. This may serve to minimize development of tolerance. It should be noted that cataplectic attacks are often refractory to treatment with stimulants. Tricyclic antidepressants (e.g., imipramine 75–150 mg/day) have been found useful in some patients with cataplexy (Arana and Hyman, 1991) (see Chapter 8). Monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine 30–75 mg/day) have also been effective in the treatment of sleep attacks in narcolepsy but are ineffective in treating cataplexy. An MAOI diet may also be especially problematic in adolescents.

Provigil (modafanil) has recently been FDA-approved as a wakefulness-promoting agent (PDR, 2001) with actions similar to other sympathomimetic medications including those of the psychostimulants, methylphenidate and amphetamine. Ongoing double-blind, placebo-controlled studies in adult ADHD patients suggest possible efficacy. Recent open-label investigation in 6- to 12-year-olds with ADHD treated with modafanil, titrated from 100–400 mg/day, revealed pharmacokinetic parameters to be consistent with those observed in adult ADHD patients (Labellarte, 2000). Modafanil has also appeared to be safe and effective in treating pediatric ADHD. Follow-up controlled studies in pediatric ADHD patients are being considered. While no recommendations as to its use in childhood ADHD patients can be made at this time, further study is clearly warranted.

Exogenous Obesity

The Physician's Desk Reference (2001) lists dextroamphetamine sulfate as indicated for use as a "short-time (a few weeks) regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy. . . ." Other stimulants have been used to inhibit appetite, but since tolerance develops to their anorectic effects within 2 weeks, they are generally too short term to be of any true value in weight loss programs (Arana and Hyman, 1991; Kaplan and Sadock, 1991). We do not recommend their use for obesity or inhibition of appetite.

ADHD in Preschool Children

Only dextroamphetamine and Adderall are FDA-approved for children under 6 years of age (but not for children under 3 years of age) (PDR, 2001). Nonetheless, prescription of psychostimulant medications for preschool-age children has increased dramatically in recent years (Zito et al., 2000). As many as 5% of pre-

school children are treated with stimulants for problematic behaviors (Gadow, 1981). Methylphenidate remains the most prescribed stimulant among all age groups, including preschoolers. To our knowledge, as of 1999 there have been six randomized controlled trials using stimulant medications (Spencer et al., 1996a; Handen et al., 1999).

Differentiating between what is and what is not pathological behavior in preschool children can be extremely difficult. Stimulant therapy, therefore, should be utilized only where other treatment modalities (behavioral modification therapy, parent management and education training, social skills training, structured preschool programs, etc.) have been unsuccessful. Nonetheless, there are clearly preschool children for whom stimulant medication is necessary.

Barkley (1988a) found that preschoolers treated with methylphenidate exhibited significantly more side effects than did older children and adolescents. The efficacy of methylphenidate in this population was observed to be equivalent to that in older children, but somewhat more variable. This has resulted in debate over the efficacy and safety of stimulants in preschool-age children. In an earlier review of the literature, Rosenberg (1987) reported that five of six published papers using methylphenidate in preschool children with ADHD found no significant benefit of methylphenidate with common problematic side effects. In children with positive outcomes, these were more variable than outcomes observed in older school-age children. In fact, many parents ultimately discontinued stimulant medication even in children who had experienced benefit on the medication. Thus, the prevailing view had not been very favorable with regards to prescribing stimulant medication in preschool age children.

However, recent investigation has begun to change this perception. Wilens and Biederman (1992) conducted a follow-up review of 130 preschool age children with ADHD from four important studies (Conners, 1975; Schleifer et al., 1975; Barkley, et al., 1984; Barkley, 1988a). In contrast to prior concerns, these studies found minimal problematic side effects when stimulants were prescribed to preschool-age children with considerable improvement in behavior. As reviewed by Barkley (1998), expert consensus opinion holds that there are strong data supporting the safe and efficacious prescribing of stimulants to preschool-age children with ADHD.

Conclusive data that would inform clinicians about a safe and effective starting stimulant dose and full stimulant dose range have yet to be collected. In the absence of such data, clinicians should start at low doses (e.g., 1.25 mg or a quarter pill of methylphenidate), increase the dose every 3 days by a quarter of a pill (e.g., 1.25 mg, 2.5 mg, 5 mg, 7 mg, and 10 mg per dose) to help decrease the risk of problematic side effects. It should be noted that starting preschoolers on lower-than-standard doses (e.g., 0.3 mg/kg/dose) may result in undertreatment (Barkley, 1998). The recently initiated National Institute of Mental Health (NIMH) Preschool ADHD Treatment Study (PATS) will start preschoolers on

1.25 mg/dose of methylphenidate (personal communication, Dr. Lawrence Greenhill, lead PATS investigator). This pioneering, critically important study will provide more definitive data on the safety, efficacy, and dosing of stimulant medications in preschoolers. Stimulant medications are not currently recommended for use in children under 3 years of age (Handen et al., 1999).

Undifferentiated Attention Deficit Disorder

This represents a residual category in which the primary feature is “problems with initiating and maintaining attention.” Barkley and associates (1991b) demonstrated that methylphenidate can decrease distractibility and improve attention span, interpersonal interactions, and responsiveness to instructions and commands, resulting in more productive and accurate academic performance. Stimulants, therefore, appear to be effective in treating attention-deficit symptoms without hyperactivity.

ADHD in Children with Conduct Disturbances

Klein et al. (1997) reported a significant reduction in antisocial behavior specific to conduct disorder in a controlled trial of methylphenidate in 84 boys with comorbid ADHD and conduct disorder. This beneficial effect persisted even when controlling for baseline ADHD symptoms.

ADHD in Children with Anxiety Disorders

Double-blind, placebo-controlled study in children with ADHD and anxiety disorders initially suggested that anxious ADHD children exhibit a significantly greater placebo response rate (Pliszka, 1992; DuPaul et al., 1994) with more side effects and poorer performance on neurocognitive testing (Tannock et al., 1995). More recent placebo-controlled investigation of 91 children with ADHD with and without comorbid anxiety (Diamond et al., 1999) found equivalent good response to methylphenidate in both groups without increased side effects in children with comorbid anxiety. Increased physiological symptoms at baseline were reported in children with ADHD and comorbid anxiety than in ADHD children without comorbid anxiety. Therefore, Diamond et al. (1999) recommended careful assessment and documentation of these symptoms prior to initiating treatment so that they are not misconstrued as medication side effects. The Multimodal Treatment Study of Children with ADHD (MTA) study (MTA Cooperative Group, 1999b) confirmed an absence of negative effects of stimulant on children with ADHD and comorbid anxiety disorders in a larger sample of children ($n = 579$).

ADHD in Children with Developmental Disabilities

In the past, clinicians were often loath to prescribe stimulants for children with developmental disabilities and intellectual handicaps, such as mental retardation (MR). There has been very little study in these populations, and it was feared that such centrally acting stimulants could exacerbate preexisting CNS anomalies and predispose children to severe side effects, especially seizures. McBride and colleagues (1986) demonstrated that methylphenidate in therapeutic doses did not lower the seizure threshold. This was confirmed by Crumrine and colleagues (1987), who found that therapeutic doses of methylphenidate in children with seizures and ADHD did not increase the likelihood of seizures. Although the data here are still limited, recent studies appear to support the cautious use of stimulants in this population. Handen et al. (1999) demonstrated methylphenidate doses of 0.3 and 0.6 mg/kg/dose to be superior to placebo in treating preschool children with developmental disabilities and ADHD. Seventy-three percent of preschool-age children with developmental disabilities and ADHD responded to stimulant medication with at least a 40% reduction in teacher-rated Conners Hyperactivity Index and/or Behar Hyperactive-Distractible scores. This rate was consistent with rates seen in school-age children with ADHD and higher than that typically seen in children with ADHD and MR. Handen et al. (1999) did, however, report a much higher rate of problematic side effects in preschool-age children with ADHD and developmental disabilities (45%) compared to rates in school-age children with developmental disabilities and preschool ADHD children without developmental disabilities. Side effects were more common in preschool ADHD children with developmental disabilities who received higher doses of methylphenidate, particularly those receiving 0.6 mg/kg/dose (Handen et al., 1999). Social withdrawal was the most common side effect of methylphenidate observed in preschool children with ADHD and developmental disabilities.

ADHD in Children with Mental Retardation

Methylphenidate response rates in school-age children with ADHD and MR range from 37 to 75% (Aman and Singh, 1982; Aman, 1982; Handen et al., 1990, 1992, 1995; Aman et al., 1991a,b, 1993). Overall response rates are decreased compared to ADHD children without MR (Barkley et al., 1993), and side effects are greater (Handen et al., 1991).

ADHD in Children with Fragile X Syndrome

This is the second-most-common known genetic cause of MR, and many children with this disorder have symptoms of ADHD that do respond to stimulants (Dulcan, 1990).

ADHD in Children with Pervasive Developmental Disorder

According to DSM-IV (American Psychiatric Association, 1994), ADHD cannot be diagnosed in the presence of pervasive developmental disorder (PDD, autism). Nonetheless, children and adolescents with PDD often exhibit the classic ADHD symptoms of hyperactivity, impulsivity, distractibility, fidgetiness, and so on. Stimulants have been found to be effective and safe when used properly in this population (Dulcan, 1990). Particular care must be used when monitoring side effects, as motor and behavioral side effects may be difficult to document. The recommendation is to start at a low dose and increase it very gradually.

ADHD in Children with Head Trauma and/or Organic Brain Disease

Brain-damaged children and adolescents often experience ADHD symptoms, including hyperactivity, difficulty in attending, distractibility, and impulsivity, and may benefit from stimulant medication (Dulcan, 1990). Seizures secondary to stimulant use are not felt to be a greater hazard in this population.

ADHD in Children with Tic Disorders (Tourette's Syndrome)

Many authorities recommend against using stimulants in children and adolescents with tic disorders and/or a family history of Tourette's syndrome (TS) (Golden, 1979; Lowe et al., 1982; Barkley, 1990; Singer et al., 1995; Peterson and Cohen, 1998; PDR, 2000). This is largely based on stimulant medications being implicated in exacerbating preexisting motor tics or causing the de novo onset of tics, including those observed in TS. This is quite relevant to clinical practice since 20–50% of TS patients have comorbid ADHD symptoms (Greenhill, 1995). Lowe et al. (1982) reported that psychostimulants exacerbated tics during maintenance treatment, while in an uncontrolled study Riddle et al. (1995) reported improvement in tics when methylphenidate was withdrawn. This has led to many experts expressing concern that stimulant use is associated with a "serious risk" of exacerbating tics (Peterson and Cohen, 1998).

Recent randomized controlled studies by several groups have, however, begun to suggest that stimulants can be safely and effectively prescribed in many ADHD patients with comorbid tic disorders (Sverd et al., 1989; Konkol et al., 1990; Sverd et al., 1992; Gadow et al., 1992, 1995a,b, 1999; Castellanos et al., 1997; Law and Schachar, 1997; Nolan and Gadow, 1997). Law and Schachar (1999) compared 91 children with and without comorbid tics who were randomly assigned to treatment with methylphenidate or placebo in a prospective 1-year study and found no difference in tics between the placebo and medication condition in patients with or without tics. Nolan et al. (1999) studied 19 children with

comorbid ADHD and chronic tic disorder that had been treated with methylphenidate or dextroamphetamine for at least 1 year. Abrupt switch to placebo did not result in change in tic frequency or severity. Specifically, tics did not worsen during the medication condition or when medication was abruptly discontinued. Thus, methylphenidate and dextroamphetamine are considered safe and efficacious treatments for many but not all children with ADHD and tic disorders (Freeman, 1994). It should also be noted that while tics occur in approximately 9% of children being treated with stimulant medication (Findling and Dogin, 1998), most of these tics do not persist, with a chronic tic disorder emerging in less than 1% of all cases (Lipkin et al., 1994).

Therefore, the emergence of tics may not necessarily mandate that the stimulant be discontinued. It is important to compare the degree to which the medication is benefiting the patient with the magnitude of the side effects. If there has been a significant reduction in the patient's behavioral problems and the tics do not interfere with the child's functioning or concern the parents, stimulant use may be continued, with close monitoring of the tics' course. Tics not uncommonly wax and wane independent of medication intervention. The parents and child should be informed that simple tics, such as the "bunny rabbit nose," buccal lingual tics, and simple picking behavior, may be transient and nonproblematic. If the decision is made to proceed with the stimulant trial, careful observation is necessary, and the subsequent development of additional tic behavior and/or coprolalia usually requires that the stimulant be discontinued.

The stimulants, particularly methylphenidate, dextroamphetamine, and Adderall, remain the mainstay of treatment for children with ADHD. Therefore, avoidance of all stimulants in favor of an alternative medication in patients with comorbid tic disorders and/or family history of tic disorders is not indicated. However, the child should be monitored very closely for tics while on stimulants, and if they develop the stimulant may need to be stopped.

It should be noted that some clinicians have suggested combining neuroleptics (see Chapter 12) and stimulants, α_2 -adrenergic receptor agonists (clonidine, guanfacine) (see Chapter 16), and stimulants for these patients. Haloperidol, pimozide in combination with stimulants are often effective in ameliorating tics (Cantwell, 1996). Newer atypical neuroleptics such as risperidone that may have a more favorable side effect than traditional neuroleptics may make such an approach more even viable. The possibility of rare methylphenidate-clonidine cardiotoxic interactions with three reports of sudden cardiac death (Cantwell, 1996) has been raised, although this remains controversial. Guanfacine, an α_2 -adrenergic agonist that may have fewer side effects than clonidine (see Chapter 16), may be another alternative to consider when combination therapy for comorbid ADHD-tic disorders is indicated. A risk-benefit analysis must always be conducted by the clinician, patient, and family. In severe cases with marked func-

tional impairment, monodrug therapy may not be possible or in the best interests of the child. Precision in neurodiagnostic assessment is critical for the safe and effective administration of medication combinations.

Reduction of Narcotic Analgesic Needs and Narcotic-Induced Side Effects

The addition of stimulants has been found to be useful in adult patients with severe cancer pain who require very high dosages of narcotics that result in intolerable sedation (Forrest et al., 1977). Dextroamphetamine sulfate, in particular, in doses of 5–20 mg/day, has been found to be effective in lowering the narcotic dosage requirements and resulting side effects. The dosage needs to be adjusted according to the patient's needs, taking into account when the pain is most acute and when it is most important for the patient to be alert. Therefore, dextroamphetamine sulfate can be given either in a single early morning dose or in divided doses, depending on the patient's requirements. We were unable to find any published evidence of stimulants being used to reduce narcotic requirements and narcotic-induced side effects in children. This may be a particularly worthy area for future investigation.

CONTRAINDICATIONS

For contraindications, see Table 5.

Psychosis

In general, stimulants are contraindicated when the patient is psychotic or has a history of psychosis, since they can rarely induce psychosis, particularly in children receiving high doses of medication (Barkley, 1990; Dulcan, 1990; PDR,

TABLE 5 Stimulant Contraindications

Absolute:
None
Relative:
Psychosis
Pregnancy
History of substance abuse in patient and/or family
Tic disorders (Tourette's syndrome) in child and/or family
History of adverse reaction to stimulants
Height/growth retardation
Cardiac/blood pressure abnormalities
Impaired liver functioning (magnesium pemoline)
Patient being treated with MAOI (infrequent in children and adolescents)

2001; Findling and Dogin, 1998; Greenhill et al., 1999). Amphetamine-induced psychosis is the model often used to explain the dopamine hypothesis of schizophrenia (Kaplan and Sadock, 1991). Indeed, the two conditions are typically best treated with antipsychotic medication. Nonetheless, the psychosis observed with dextroamphetamine is dose-related and involves enormous doses of 300 mg per dose compared to a typical single dose of 10 mg for a child with ADHD (Angrist, 1972; Greenhill et al., 1999). In general, however, stimulant medication should be avoided or used with great caution in psychotic children and adolescents.

It should be noted that recent investigation suggests that mania or bipolar disorder can be misdiagnosed as ADHD and that the two conditions can also coexist (Biederman et al., 1998). This is an area of active investigation, and definitive treatment guidelines are not available at present. Caution is clearly indicated when prescribing psychostimulants to patients with comorbid bipolar disorder. Euphoric side effects from stimulants have been reported in adolescents but not in younger children. Nonetheless, there are insufficient data at present to determine whether prescribing psychostimulants to prepubertal patients with bipolar disorder and ADHD can exacerbate manic symptomatology. Volkow et al. (1998), using positron emission tomography (PET), demonstrated that oral methylphenidate does not cause euphoria. Carlson et al. (1999) reported that adolescents with ADHD and comorbid bipolar disorder were not worsened by treatment with stimulants.

When ADHD and bipolar coexist, we advise stabilizing the bipolar condition pharmacologically before administering psychostimulant medication. Determining whether the two conditions coexist or whether there is one underlying condition can often be difficult, particularly in prepubertal children. A single cross-sectional evaluation is often not sufficient to make a definitive diagnosis. Longitudinal assessment is indicated. This underscores how precision in diagnosis is critical in making the appropriate treatment intervention. Lithium and anti-convulsants such as valproic acid are not effective in treating ADHD but can be quite effective in treating bipolar disorder. Conversely, psychostimulants are the drugs of choice in treating ADHD but can exacerbate or precipitate mania in bipolar patients and those at risk for developing bipolar disorder.

Pregnancy

Because stimulants cross the placenta, they are virtually never indicated during pregnancy (Dulcan, 1990; Arana and Hyman, 1991; PDR, 2001).

History of Substance Abuse

Since amphetamines have long been a popular drug of abuse with potentially severe consequences, including psychosis, concerns about risks for psychostimulant abuse have been voiced. Many children with ADHD have coexisting opposi-

tional defiant disorder or conduct disorder, conditions associated with a significantly increased risk for recreational drug abuse (Kaplan and Sadock, 1991). Methylphenidate, dextroamphetamine, and Adderall are classified as Schedule II drugs, the most restrictive class of drugs considered to be medically useful. There has been a particularly dramatic increase in stimulant production and prescriptions in recent years (Goldman et al., 1998; Zito et al., 2000). Given the increased risk for substance abuse in patients with ADHD and their being treated more commonly with stimulants than ever before, concerns have been voiced about these medications being abused, diverted, sold, and increasing the risk for abuse of other recreational drugs (Findling and Dogin, 1998; Greenhill et al., 1999). It is, therefore, essential to monitor both the patient and family closely when stimulants are prescribed. Nevertheless, there are no data to support the view that stimulants, when prescribed correctly, lead to the increased use/abuse of recreational drugs (Gadow, 1981). It should be noted that the usual stimulant high did not occur in three adolescents who attempted to intranasally snort once-daily extended release tablets of oros methylphenidate (Concerta) (Jaffe, 2002). Further study is warranted to determine whether once-daily extended release stimulant preparations may have reduced risk for abuse.

Recent PET scan data (Volkow et al., 1998) have demonstrated that therapeutic doses of oral methylphenidate have a significantly slower absorption, dopamine transporter occupancy in the brain, and clearance than intravenously administered cocaine. Volkow et al. (1998) also found that oral methylphenidate did not induce euphoria. Methylphenidate is mentioned only 1/40 as often as cocaine in the emergency room setting according to data from the Drug Abuse Warning Network (Goldman et al., 1998). Therefore, while ADHD is associated with an increased risk for drug abuse, when prescribed at therapeutic dosages psychostimulants do not appear to increase the risk of abuse (Greenhill et al., 1999).

Antidepressants such as desipramine, imipramine, or bupropion or α_2 -adrenergic receptor agonists such as guanfacine or clonidine may be preferable, however, if the patient or family members are at particularly high risk for abusing or selling stimulants. Bupropion, for example, under the trade name Zyban, is FDA-approved for smoking cessation in adults. Bupropion is also marketed under the trade name Welbutrin and is FDA-approved for treating adults with major depressive disorder. Although not approved for use in pediatric smokers, its investigation in pediatric smokers and potentially other substance abusers with ADHD is warranted. Still, antidepressants and α_2 -adrenergic receptor agonists are not without their own risks and may have significant disadvantages as a first-line treatments for children and adolescents (see Chapters 8, 10, and 16).

Tic Disorders (Tourette's Syndrome)

As described above, recent investigation suggests that stimulants may be prescribed safely and effectively in ADHD patients with comorbid tic disorders.

Nonetheless, before initiating a stimulant trial, it is important to screen for the presence of tics in both the child and the family. While comorbid tics and/or a family history of tics does not preclude the use of stimulants in children and adolescents, it does mandate closer monitoring for evidence of tics while the patient is receiving stimulant medication (see Indications).

History of Adverse Reactions

As with any medication, stimulants generally should not be used in children and adolescents who have a history of adverse reactions to their use.

Height/Growth Retardation

Reports from the early 1970s indicated that methylphenidate and dextroamphetamine could suppress a child's height and weight (Safer et al., 1972; Safer and Allen, 1973). Gittleman-Klein et al. (1988) observed small decreases in weight during a short-term methylphenidate trial. Anorexia is one of the most common side effects reported with methylphenidate treatment (Barkley et al., 1990; Jacobvitz et al., 1990; Ahmann et al., 1993) so that weight and height should be monitored while a patient is on stimulant medication. There have also been reports of children experiencing delayed height gain while taking stimulants related to both the medication dose and the length of time the child is receiving medication (Barkley, 1990; Dulcan, 1990). It has been further suggested that amphetamine derivatives, i.e., dextroamphetamine and Adderall, may suppress growth more than methylphenidate or pemoline does, and this effect may be most often seen during the first year of treatment. The eventual height and weight of children treated with these medications are not significantly affected, however, and a rebound growth or habituation to the growth-suppressing effect produced in the first year is usually noted (Mattes and Gittelman, 1983; Klein and Mannuzza, 1988). Concern has also been raised that adolescents between 15 and 18 years of age, the period of epiphyseal closing, who continue to receive stimulant medication may experience a permanent decrease in their ultimate height of over 1 inch (Dulcan, 1990). Recent investigation (Schertz et al., 1996) also demonstrated that height-adjusted weight can help predict children most likely to exhibit weight loss while on stimulant medications. Specifically, height and weight loss may be more common in taller and heavier children than thinner and smaller children (Mattes and Gittelman, 1983; Klein and Mannuzza, 1988; Schertz et al., 1996). It has been hypothesized that the height loss may be the result of an alteration in cartilage metabolism rather than in growth hormone production and metabolism (Klein and Mannuzza, 1988; Dulcan, 1990). Recommendations to minimize the risk have included choosing an alternative medication for children who fail to thrive, monitoring weight and height very carefully, and stopping or decreasing the dose of the stimulant if any significant delay is noted. The use of drug holidays (sum-

mer vacation, Christmas vacation, etc.) has also been recommended, as is using the minimum required dose necessary to improve behavior.

Subsequent clinical investigation has demonstrated that stimulant use does not result in a significant decrease in the ultimate height of most children (Klein and Mannuzza, 1988). Mannuzza et al. (1991) conducted a prospective follow-up study into adulthood of children treated with stimulant medications and found no significant height loss. Spencer et al. (1996b) also found that ADHD children, irrespective of stimulant status, exhibited slower growth than healthy children. Thus, growth effects may be related to the impact of the illness itself rather than a specific medication side effect.

Cardiac/Blood Pressure Anomalies

Because of their sympathomimetic properties, stimulants can increase blood pressure and pulse rate (Sprague and Sleator, 1977; Brown et al., 1984; Greenhill, 1995) and should not be prescribed in children with baseline hypertension and/or tachycardia (Barkley, 1990; Dulcan, 1990). Instead, a medication such as guanfacine may be preferable. When tachycardia and/or hypertension occurs after the initiation of a stimulant trial, the effects on pulse and blood pressure are usually not clinically significant and often do not require the medication to be discontinued (Dulcan, 1990). At 0.3 mg/kg/dose of methylphenidate, there is usually little if any change in heart rate or blood pressure (Aman and Werry, 1975; Brown et al., 1984). It should be noted, however, that African American adolescents being treated with methylphenidate may be at significantly increased risk for experiencing increases in diastolic blood pressure (Brown and Sexson, 1988). Careful monitoring is, of course, necessary, and additional investigation, including an electrocardiogram (EKG) and/or cardiology consultation, is recommended in the event of significant increases in blood pressure/heart rate with stimulant administration. Again, we wish to reiterate that increased heart rate is a direct effect of these agents and thus is present in virtually all medicated children but is typically not clinically significant. Increases to levels that are clinically significant and of concern to the patient and physician are uncommon. Safer (1997) published a very comprehensive review showing that statistically significant but clinically insignificant elevation in cardiovascular parameters show tolerance within 6 weeks.

Impaired Liver Functioning

Impaired liver functioning and frank hepatic injury have been observed in patients being treated with the stimulant pemoline (Barkley, 1990; Nehra et al., 1990; Wroblewski et al., 1992; Berkovitch et al., 1995). Hepatitis with elevated liver function tests (LFTs), e.g., increased serum transaminase, is observed in nearly 3% of children treated with pemoline (Barkley, 1990). Safer et al. (2001) recently

reviewed premarketing clinical trials with pemoline in the 1970s and reported that liver enzymes abnormalities were noted in 1–3% of children on pemoline maintenance treatment, in six of six children on pemoline rechallenge and in two of two biopsies. During a 14-year period (1975–1989), 12 cases of jaundice and 6 deaths associated with pemoline administration were reported to the FDA. The author noted, however, that prescribing physicians did not become generally cognizant about pemoline hepatotoxicity until December, 1996, and that pemoline prescriptions continued to increase until 1997 (Safer et al., 1997). The mechanism for the increase in LFTs and cause of liver failure are unknown. Berkovitch et al. (1995) reported abnormal LFTs in 44 children receiving pemoline. Eleven of these patients experienced hepatic failure. While hepatotoxicity associated with pemoline treatment is usually reversible and relatively mild, this complication does not always remit upon discontinuation of the medication. Therefore, it is essential that LFTs be checked in all children for whom pemoline use is being considered and at least every 6 months during treatment with the drug (Barkley, 1990). Three deaths due to liver failure have been attributed to treatment with pemoline with recent investigation suggesting that the medication clearly increases the risk of a child's developing hepatic failure (Berkovitch et al., 1995). Thus, pemoline is not considered a first-line agent in the treatment of ADHD (Stevenson and Wolraich, 1989). The manufacturer, Abbott, recommends that biweekly liver function tests be taken for all children on pemoline, further reducing the feasibility of its being used. Indeed, many clinicians are opting to use antidepressants, i.e., bupropion, desipramine, or α_2 -adrenergic receptor agonists, i.e., guanfacine instead of pemoline, if a child has failed methylphenidate and dextroamphetamine/Adderall trials.

It should be noted that while there have been reports of hepatic tumors in rodents treated with high oral doses of methylphenidate 4–47 mg/kg (Dunnick and Hailey, 1995), this has never been observed in children treated with stimulants. Thus, LFT monitoring is not indicated when methylphenidate and dextroamphetamine or Adderall is prescribed.

Patients on MAOIs

Children and adolescents are very rarely prescribed MAOIs due to the strict dietary restrictions and the lack of documented efficacy in this population. Nonetheless, stimulants should not be used within one week to 10 days of the discontinuation of an MAOI.

Seizures

There is no increased frequency of seizures with the use of stimulants (Crumrine et al., 1987). Careful monitoring is required when co-administering stimulants and anticonvulsants as stimulants tend to increase the blood levels of these medi-

TABLE 6 Stimulant Side Effects

Common:
Insomnia
Decreased appetite
Gastrointestinal pain
Irritability
Increased heart rate (clinically insignificant)
Paradoxical worsening of behavior
Uncommon:
Psychosis
Euphoria/mania
Sadness/isolation
Major depressive episodes
Cognitive impairment
Growth retardation
Tic disorders (i.e., Tourette's syndrome)
Increased heart rate (clinically significant)
Impaired liver functioning (pemoline only)
Increased blood pressure
Dizziness, lethargy, fatigue
Nausea, constipation
Rash/hives
Hyperacusis
Formication
Necrotizing angitis brain (IV amphetamine)
Neuroleptic malignant syndrome?

cations. Nonetheless, stimulants can be administered safely and with good success in children with seizure disorders.

SIDE EFFECTS

Severe side effects occur in 4–10% of children treated with stimulants (Greenhill et al., 1999). Side effects are listed in Table 6.

Insomnia

Insomnia is a very common side effect observed with stimulant use. Barkley et al. (1990) found that over 50% of 82 ADHD children receiving methylphenidate (0.3 and 0.5 mg/kg) developed insomnia, a decrease in appetite, nervousness, irritability, and increased crying. Fortunately, these side effects are usually transitory and mild. In fact, in the Barkley et al. (1990) study, many of these “side

effects'' were present during the placebo phase of the trial. The difference in side effects between the two phases was not reported as being significant. Kent et al. (1995) also reported no additional insomnia problems when a third dose of methylphenidate was added in the mid-afternoon in children who had been receiving the medication twice per day. In a comprehensive review of stimulant treatment conducted by the Agency for Health Quality Research at McMaster University (Jadad et al., 1999), including findings from 2404 studies in the stimulant literature, very few of the high-quality controlled studies were able to substantiate increased sleep difficulties as many children with ADHD have major sleep difficulties without medication. Reported side effects may also be a manifestation of the underlying disruptive behavior disorder, a rebound drug effect, a direct effect, or a primary sleep disturbance. If the sleep disturbance dissipates, the stimulant can be continued. On the other hand, if the insomnia does not reverse, further clinical and/or laboratory investigation is necessary, and the stimulant may have to be discontinued.

Anorexia/Weight Loss

Anorexia and weight loss are common but are usually short-term side effects. The amphetamine compounds dextroamphetamine and Adderall appear to suppress weight more than methylphenidate or pemoline. Anorexia and weight loss are said to be minimized by giving the stimulants after meals. Chan et al. (1983) demonstrated that methylphenidate bioavailability was increased if taken with a meal, including milk. More recently, during the development of the extended-release stimulant preparations, some of the early prototypes were absorbed more poorly with a high-fat meal than a low-fat meal, resulting in redesign of the preparation to yield high stimulant bioavailability regardless of fat content of the diet (Dr. Lawrence Greenhill, personal communication). It should also be kept in mind that children with ADHD are often notoriously poor eaters prior to receiving stimulant medication.

Irritability

Irritability is also a frequent short-term side effect. It is not always easy to tell whether the irritability is a side effect of the medication or a manifestation of the underlying disorder, since the presentation is usually the same in both cases. Drug A/B trials to determine whether or not the child is more irritable on stimulant medication are often informative. If this is not possible, observing the patient while off the medication and being monitored by teachers and parents can be helpful. Recent double-blind, placebo-controlled investigation of methylphenidate in 253 children showed that irritability actually decreased as stimulant dose increased (Greenhill et al., 2001).

Dysphoria/Social Isolation

Children on stimulants very commonly are reported as looking “sadder.” This may be due to a drug effect or may simply arise from the fact that the child at baseline was so hyperactive that the less hyperactive behavior may lead others to think that he or she might be depressed. This state requires careful monitoring since, although dysphoria with tearfulness and intermittent sadness is usually a short-term side effect, it may persist during treatment or after long-term treatment has discontinued. Poor self-esteem is also not uncommon in ADHD patients and may also suggest depression. Finally, ADHD itself may increase the risk for developing comorbid mood disorders such as major depression and bipolar disorder.

Abdominal Pain

Children frequently report abdominal pain while initially on stimulants, but this usually disappears with time. When using pemoline, however, LFTs should be drawn to rule out hepatocellular injury.

Decreased Cognitive Ability

Sprague and Sleator (1977) suggested that methylphenidate has a U-shaped dose-response curve in the cognitive domain. The authors suggested that there was a dissociation of cognitive dose-response curves from those in the social domain. As a result, the authors suggested that children with ADHD have an optimal response at 0.3 mg/kg/dose of methylphenidate. This type of group response has not been replicated (Rapport, 1989). This remains an area of some controversy.

Impairment in cognitive ability appears to be more common when stimulants are used at high doses (e.g., methylphenidate dosages > than 1 mg/kg/dose) (NIH Consensus Statement on ADHD, 2000). Standard dosages of between 0.3 b.i.d. and 0.69 mg/kg b.i.d. do not typically to cause cognitive depression (Pelham and Milich, 1991).

Increased Hyperactivity

While 70–80% of children treated with stimulants exhibit significant improvement in behavior, there have been reports of children becoming more hyperactive and/or “behavioral rebound” occurring on stimulant medications. Johnston and colleagues (1988) found that this effect is quite variable during the time the children are on medication and that such “rebound” rarely results in the stimulant’s having to be discontinued. Each case must be considered separately. One option is to decrease the lunchtime or early/mid-afternoon dose. Another option is to decrease the dose to the previously tolerated dose and observe whether that dose is sufficient to ameliorate the target symptoms. It should be noted that just because a child shows this effect with one stimulant (e.g., methylphenidate), this does

not mean that the child will exhibit the same behavior rebound with another stimulant trial (Elia et al., 1991).

Motor Tics, Tourette's Syndrome

These side effects are uncommon, but potentially severe. Prior to starting a stimulant, all patients and their families must be screened for the presence of tics, adventitious movements, and Tourette's (see Contraindications).

Growth Suppression

See Contraindications.

Hypertension/Tachycardia

Brown and Saxon (1989) observed that African American adolescents treated with methylphenidate may be at increased risk for diastolic blood pressure elevation. The effects on blood pressure were statistically but not clinically significant. Blood pressure and pulse changes in children are extremely variable and frequently, with careful monitoring, do not require cessation of the stimulant. Since this effect almost always produces tachyphylaxis, monitoring of all vital signs is essential. It is, however, rare that the stimulant will have to be discontinued, and often the symptoms do not persist.

Psychosis

Paranoid psychotic complications in adults ingesting large doses of amphetamines have been well documented. Ney (1967) first reported the occurrence of psychotic phenomena, including auditory, visual, and tactile hallucinations in an 8-year-old receiving therapeutic dosages of dextroamphetamine. Moreover, Lucas and Weiss (1971) observed methylphenidate hallucinosis in a 10-year-old boy receiving therapeutic dosages of methylphenidate and a 15-year-old girl who took an excess of methylphenidate. Whenever stimulants are administered, careful monitoring for thought disorder/psychosis is mandatory. If psychosis occurs, the stimulant is often best discontinued and a different class of medication utilized (e.g., antipsychotics or antidepressants).

Chemical Hepatitis/Hepatocellular Injury

Impaired liver functioning is seen only with pemoline, and the resulting chemical hepatitis and hepatic failure is not always reversible upon discontinuing the medication. Thus, it is essential to check LFTs prior to starting pemoline. After initiation of treatment, LFTs should be checked at least every 6 months. There are some who recommend checking LFTs every 3 months for the first year and then every 6 months after the first year of treatment. If the patient exhibits any side

effects, such as jaundice or abdominal pain, stat LFTs should be drawn and the medication suspended. Abnormal LFTs mandate that the pemoline be held. If the clinician is suspicious of the validity and reliability of the results of the LFTs, they may be repeated. Consistent alterations in LFTs, however, preclude pemoline's use.

Rare Side Effects

Nausea/vomiting, constipation, dizziness, lethargy, fatigue, nightmares, anxiety, rash/hives, hyperacusis, formication, and fearfulness may be observed, though rarely, as a result of stimulant use. Necrotizing angitis is a very rare complication resulting from intravenous (IV) amphetamine abuse. Sallee et al. (1989) reported that choreiform movements occur in some children treated with pemoline. Battaglia et al. (1987) demonstrated a loss of serotonin reuptake sites in rats administered high-dose 25 mg/kg subcutaneous injections of dextroamphetamine, methylphenidate, methamphetamine, and 3,4-methylenedioxymethamphetamine. This effect has not been reported in children treated with stimulants or with the dosages typically administered to children.

Butte et al. (1999) reported decreased total awake energy expenditure and physical activity in 31 children being prescribed stimulant medication for ADHD. This included less energy used when the child was doing homework, exercising on a stationary bicycle, at rest, and when viewing a movie. The total activity while awake was lower in children while on the medication and resulted in the decreased energy expenditure. However, basal metabolic rate, utilization of fuel as measured by calorimetry, and metabolic rates at sleep were not altered by stimulant medication. The clinical implications of these findings remain to be elucidated.

Decreased Seizure Threshold

There is no evidence that stimulants lower the seizure threshold (Crumrine et al., 1987).

Increased Recreational Use/Abuse of Drugs

There is no evidence that stimulants, when prescribed correctly, result in an increased propensity to use/abuse recreational or prescription drugs or that they increase physical and psychological dependence on stimulants (Gadow, 1981; Dulcan, 1990) (see also Contraindications).

Neuroleptic Malignant Syndrome

There was a recent report of a child on venlafaxine and methylphenidate who was found to have developed the neuroleptic malignant syndrome (PDR, 2001) (see package insert for Concerta).

OVERDOSE

An overdose of stimulants is less dangerous than overdosing with some other psychotropic medications, such as tricyclic antidepressants and lithium. Nonetheless, children and adolescents with ADHD and/or conduct disorders have a higher rate of suicide attempts than do children and adolescents without these disorders. Moreover, ADHD also carries an increased risk for major depression and bipolar disorder, conditions that are also associated with an increased risk for suicidal behavior. Thus, careful monitoring is required when these medications are prescribed. Overdosing with stimulants results in autonomic hyperactivity secondary to their sympathomimetic effects, with resulting hypertension, hyperthermia, and tachycardia. Psychosis and/or toxicity may also occur. An overdose may result in death because of hypertensive, hyperthermic, cardiovascular, or epileptic complications.

Stimulant overdose is a medical emergency and requires urgent treatment. Paranoid psychosis is usually best treated with the antipsychotic chlorpromazine, 50 mg PO/intramuscularly (IM) four times a day, since it blocks both dopamine and α -adrenergic receptors, thereby serving as both an antipsychotic and an antihypertensive (Arana and Hyman, 1991). Severe hypertension and tachycardia are best treated with propranolol, 1 mg IV, every 5 minutes with a maximum dose of 8 mg (Arana and Hyman, 1991).

When the hypertension is mild, haloperidol 5 mg b.i.d. is probably a better choice, since it has fewer anticholinergic and sedating properties than does chlorpromazine. On the other hand, if extra sedation is necessary because of the psychosis, the benzodiazepines are an excellent, safe alternative. Lorazepam, 1–2 mg PO/IM, is the best choice since it is the only benzodiazepine with reliable IM absorption and is relatively short-acting (Arana and Hyman, 1991). Any psychosis and delirium should clear within a few days if properly treated.

Finally, if the patient is unconscious or having seizures, maintaining an adequate airway, breathing, and circulation (ABCs) is crucial. High fevers require appropriate medical management. Seizures can be treated with lorazepam or diazepam.

ABUSE

The practicing clinician should be cognizant of the significant abuse potential of stimulants. The amphetamine compounds dextroamphetamine and Adderall have the highest risk for abuse, with methylphenidate having a lower risk and pemoline the lowest risk for abuse of all the stimulants. Amphetamine abuse, both orally and IV, has been reported with severe consequences (necrotizing angitis of the brain).

The stimulants produce a sense of euphoria that initially may be quite pleas-

ing to adolescents with ADHD and/or conduct disorders who commonly suffer from feelings of low self-esteem and who are also at increased risk for mood disorders including major depression and bipolar disorder. Patients with ADHD and conduct disorders are at increased risk for substance abuse independent of a possible psychostimulant effect. It is important to note that persons taking methylphenidate and amphetamine compounds quickly become tolerant to their euphorogenic and sympathomimetic effects. However, tolerance to the beneficial effects of these medications on ADHD symptoms is not seen in children and adolescents treated effectively with therapeutic doses. Stimulant abusers who become tolerant to high doses of stimulants can tolerate doses that could seriously harm or kill persons without such tolerance. The practicing clinician should be alert for the following signs and symptoms when stimulants are taken in large nontherapeutic quantities.

1. Sympathomimetic overload (hypertension, tachycardia, dry mouth, pupillary dilation)
2. Stereotyped behaviors
3. Irritability/emotional lability
4. Paranoia/formication

Chronic abuse looks much like schizophrenia. Characteristic signs and symptoms include:

1. Psychosis
2. Auditory/visual/tactile hallucinations
3. Ideas of reference

Psychological withdrawal after stimulants have been abused is common, although physical withdrawal does not occur. Careful monitoring for a resulting dysphoria and/or major depressive episode with feelings of hopelessness and suicidal ideation is important.

DRUG INTERACTIONS

For important drug interactions, see Tables 7 and 8.

Three cases of sudden death have been reported in children on clonidine-methylphenidate combination therapy, but whether these medications played any role in the deaths is unknown. Many children continue to be treated with this combination without incident. Nonetheless, some clinicians are reluctant to prescribe methylphenidate and clonidine together until there is more information. Some prescribe guanfacine with methylphenidate. We recommend close monitoring of vital signs if a clonidine-methylphenidate combination is administered. A baseline EKG and cardiograms or rhythm strips after each dose increase is also recommended until a stable dose regimen is obtained. The clinician should moni-

TABLE 7 Methylphenidate Drug Interactions

Inhibits metabolism of:
Anticoagulants (i.e., warfarin [Coumadin])
Anticonvulsants (Phenobarbital, phenytoin [Dilantin], primidone [Mysoline])
Phenylbutazone (Butazolidin)
Heterocyclic antidepressants (i.e., amitriptyline, Elavil)
Decreases hypotensive effect of:
Guanethidine
In combination with Imipramine can cause:
Confusion
Mood lability
Aggression
Agitation
Psychosis
Potentiates effect of:
All sympathomimetic medications (i.e., ephedrine)
Recreational stimulants (cocaine)
Metabolism is slowed by:
MAOIs
Idiosyncratic:
Clonidine?

tor closely for any signs or symptoms of cardiac problems such as chest pain, dizziness, etc.

The interaction of pemoline with other medications has not been studied in humans. Careful monitoring of patients receiving pemoline while on other drugs, particularly drugs with CNS activity, is required.

INITIATING AND MAINTAINING TREATMENT

Available preparations of psychostimulants and costs are shown in Table 9.

Because of their safety and efficacy, stimulants are considered the drugs of first choice for patients with ADHD (American Academy of Child and Adolescent Psychiatry, 1991). While only dextroamphetamine and Adderall are FDA-approved for preschool age children (3 years and older), the stimulants have been found to be safe and effective in treating preschool-age children and adolescents (Klorman et al., 1987; Barkley, 1988b; Brown and Sexson, 1989).

Methylphenidate, dextroamphetamine, Adderall (previously called Obe-trol), and pemoline are the most prescribed stimulants (Stevenson and Wolraich, 1989; Zito et al., 2000). Prior to initiating the psychostimulants, children and adolescents should have a physical examination, with special attention paid to

TABLE 8 Dextroamphetamine/Adderall Drug Interaction

Inhibits:
Beta-adrenergic blockers (propranolol)
In combination with TCAs, MAOIs, inhibiting antidepressants, narcotics:
Effects of both medications increased
Delays absorption of:
Phenytoin
Phenobarbital
Ethosoximide
Decreases hypotensive effect of:
Guanethidine
Absorption lowered by:
GI-acidifying agents
Absorption increased by:
GI-alkalinizing agents
Renal clearance increased by:
Urine-acidifying agents
Renal clearance decreased by:
Urine-alkalinizing agents (i.e., thiazides)
Increases:
Plasma corticosteroid levels
May alter:
Urinary steroid measurements
Insulin requirements

heart rate, blood pressure, height, and weight. A baseline screen for abnormal involuntary movements, including tics, should be performed. It is important to elicit any family history of motor movement tic disorders. Because the stimulants cross the placenta, they should not be prescribed during pregnancy, and so a pregnancy test and evaluation for adequate contraceptive use are essential in all women of childbearing age. When prescribing methylphenidate or dextroamphetamine and Adderall, laboratory tests are generally not necessary. When pemoline therapy is to be initiated, LFTs are mandated, as nearly 3% of patients placed on pemoline will develop a chemical hepatitis that is not always reversible when the medication is discontinued (Dulcan, 1990; Nehra et al., 1990; Berkovitch et al., 1995).

When children and adolescents are treated with stimulants, they should be monitored at each visit for any involuntary movements/tics by observation and/or history. Whenever the dose is increased, it is important to check blood pressure, pulse, height, and weight. In addition, it is advisable to record height and weight at regular 3- to 4-month intervals. LFTs should be drawn every 6 months when

TABLE 9 Available Preparations and Cost of Psychostimulants

	Commercially available preparations	Dosage form	Average cost/day
Dextroamphetamine	Generic (dextroamphetamine sulfate)	5 mg (scored), 10 mg (scored) tablets	\$ 0.12
	Dexedrine	5 mg (unscored), 10 mg (unscored) tablets; 5 mg/5 mL elixir	\$ 0.72
	Dexedrine spansules (sustained release)	5 mg, 10 mg, 15 mg capsules	\$ 0.82
Dextro and levoamphetamine	Adderall	5 mg (unscored), 10 mg (scored), 20 mg (scored)	\$ 2.02
Methylphenidate	Generic	5 mg, 10 mg, 20 mg tablets	\$ 0.77
	Ritalin	5 mg (unscored), 10 mg (unscored), and 20 mg (unscored) tablets	\$ 1.02
	Ritalin—SR (sustained release)	20 mg tablet	\$ 1.06
	Metadate—ER (extended release)	10 mg and 20 mg tablets	\$ 2.32
	Methylin	5 mg (unscored), 10 mg (scored), 20 mg (scored) tablets	\$ 1.15
	Concerta (extended release)	18 mg and 36 mg tablets	\$ 2.60
	Pemoline	Cylert	18.75 mg, 37.5 mg, 75 mg (scored) tablets, 37.5 mg chewable (scored) tablets

using pemoline. Some clinicians prefer to draw LFTs every 3 months during the first year of treatment and every 6 months thereafter. Children and adolescents should have an annual physical examination by their pediatrician and family practitioner.

When prescribing psychostimulants it is critical to determine the lowest dose with maximal efficacy and minimal toxicity since most medication side effects are dose dependent (Greenhill, 1995). Precise diagnostic assessment with

clear identification of target symptoms is critical. When treating children it is important to review data from the child, parents, and school (Dulcan, 1990; Wilens and Biederman, 1992).

SPECIFIC AGENTS AND INDICATIONS

Methylphenidate

Methylphenidate remains the drug of choice in the treatment of ADHD in children and adolescents and is the most commonly prescribed psychostimulant (Zito et al., 2000). It is one of the safest medications in all of child psychiatry, with a quick onset of action and a very short half. It is effective in 70–80% of children and adolescents. While its effects may be more variable in preschool age children in whom the medication is not FDA-approved, it can be administered safely and effectively in this population. Moreover, the dramatic increase in stimulant prescriptions, particularly methylphenidate in preschool age children (Zito et al., 2000) underscores that diagnostic rigor and comprehensive assessment are especially critical in this age group. Diagnosing ADHD in preschoolers can be difficult and we advise using stimulant medication only after environmental and behavioral/parent management interventions prove unsuccessful and/or the behavior is so dangerous and problematic that it represents a threat to the child or other persons safety.

Dosage and Administration

The starting dose of methylphenidate is usually 0.3 mg/kg/dose. Whenever possible, a simple drug A/B trial is ideal for determining whether or not the child truly benefits from the medication and what the most effective dose is (Table 4 shows how to perform a drug A/B trial). When it is not possible to perform such a trial, initiating treatment at a dose of 0.15 mg/kg and increasing it gradually, monitoring closely for efficacy versus toxicity, is recommended. In general, a dose exceeding 1 mg/kg is not recommended since laboratory tests have shown cognitive impairment resulting in problems with concentration and learning at such high doses (Sprague and Sleator, 1977; Brown and Sleator, 1979). Optimal doses are usually achieved between 0.3 and 0.8 mg/kg given three times per day (Pelham et al., 1985; Dulcan, 1990; Amaya-Jackson and Cantwell, 1991; Barkley et al., 1991b). If this range is unsuccessful and the child suffers no side effects, the dose may be gradually increased to a maximum of 1 mg/kg/dose. Dosages greater than 1 mg/kg are not recommended because of unacceptable side effects. It should be noted that in the Multimodel Treatment Study of Children with ADHD (MTA) study of methylphenidate, the investigators did not exceed 0.8 mg/kg/dose for a child weighing less than 25 kg. Thus, they set the top methyl-

TABLE 10 Clinician's Guide to Using Stimulants for ADHD in Children and Adolescents**Methylphenidate schedule:**

Not approved for children <6 years old.

Six years and older: start with 5 mg twice a day, increase by 5–10 mg/week to maximum dose not to exceed 60 mg.

Optimal dose 0.3–0.8 mg/kg two to three times per day (total daily dose: 0.9–2.4 mg/kg/day). Do not exceed 1 mg/kg/dose.

For Concerta initiate dose at 18 mg/day and titrate by 18 mg increment/week to maximum of 54 mg/day.

Dextroamphetamine/Adderall schedule:

Not approved for children <3 years.

3–5 years: start with 2.5 mg/day increased by 2.5 mg/week, adjust to best tolerated dose.

6 years and older: start with 2.5 mg twice a day increased by 5 mg/week to maximum dose not to exceed 40 mg.

Optimal dose 0.15–0.5 mg/kg two to three times daily (total daily dose: 0.3–1.5 mg/kg/day).

Pemoline schedule:

Not approved for children <6 years old.

6 years and older: start with 37.5 mg/day, increase by 18.75 mg/week to maximum daily dose of 112.5 mg/day.

phenidate dose for a 20 kg child at 15 mg or about 0.75 mg/kg (Greenhill et al., 2000) (Tables 10 and 11).

For the practicing clinician, this generally translates into treating children who weigh less than 30 kg with 5 mg after breakfast and 5 mg after lunch (Findling and Dogin, 1998). For very young children, the tablets can be broken in

TABLE 11 Dose Ranges

Drug	Therapeutic dose range	Usual dose range	Extreme dose range
Methylphenidate	0.15–0.8 mg/kg/dose	20–40 mg/day	40–60 mg/day or higher
Concerta	18–54 mg/day	36–54 mg/day	>54 mg/day
Dextroamphetamine/Adderall	0.08–0.3 mg/kg/dose	10–20 mg/day	30–40 mg/day
Pemoline	0.6–4 mg/kg/day	37.5–112.5 mg/day	>112.5 mg/day

quarters or half so that 1.25, 2.5, 5, 7.5, and 10 mg per dose can be given. In children who weigh more than 30 kg, a starting dose of 10 mg after breakfast and 10 mg after lunch can be given. However, many clinicians opt to start at 5 mg b.i.d. dosages in these children in an attempt to reduce risk for problematic side effects. Single doses above 20 mg are generally not recommended. Dosages should be increased gradually by 5–10 mg/week or every other week (PDR, 2001).

Methylphenidate is typically effective for 3–4 hours after administration (Findling and Dogin, 1998). Doses are increased in the morning and at lunchtime every week/every other week, so that at least 5 full days of the child's daily report card and parent-teacher Conner's Rating Scales can be assessed. Individual adjustment of the dose is often required. For instance, if the child is having problems with hyperactivity on the school bus, a dose 30 minutes before he or she gets on the bus is suggested. On the other hand, if the problems with behavior do not manifest themselves until the first school period or shortly after it, it may be best to give the child his or her dose when he or she gets to school (or just before). In addition, if the effect of the methylphenidate seems to be wearing off at about 10:30 or 11:00 a.m., raising the morning dose or giving the second dose at 10:00 or 11:00 a.m. may be advisable. Thus, it is crucial to determine when and in what setting the behavior is most problematic. Sometimes, a small afternoon dose is required. This should not be given later than 4:00 p.m. since exacerbation of behavior may result. Many physicians prescribe a smaller dose at this time than the two earlier doses. Recent investigation also suggests that afternoon doses of methylphenidate are not usually associated with insomnia and can often be very effective in improving the child's behavior (Kent et al., 1995; Stein et al., 1996).

Determination of whether or not the child requires medication on weekends or after school can be difficult but is important. If the main problems are in school and the parents feel that the behavior at home is not a problem, then weekend doses may not be necessary. On the other hand, if significant problems with behavior are occurring after school and/or on weekends, medication may be indicated during these times. In some cases, p.r.n. doses of the stimulant may be warranted—if, for instance, the family is going to a function where the child has had significant difficulty in the past. Reassessment of medication needs is essential on at least a yearly basis, if not more often. Taking the child off medication over summer and Christmas vacations is a good way to assess the continued need for stimulants, as well as to minimize the risk of developing tolerance. A drug A/B trial can also be performed a year after the initiation of the stimulant, particularly if there is a question as to whether the stimulant is needed or whether the dose should be altered. It should be noted, however, that medication is often necessary for weekend recreational activities involving peers (e.g., soccer matches, Little League baseball games, church, etc.).

Dextroamphetamine/Adderall

When methylphenidate is unsuccessful, dextroamphetamine or Adderall is usually the next line of treatment. As with methylphenidate, 70–80% of children and adolescents will respond to dextroamphetamine or Adderall. Unfortunately, there is no way to predict which child will respond to which medication. Moreover, the fact that a child does not respond to methylphenidate does not mean that he or she will not respond to another stimulant. If a child has previously responded to a particular stimulant or has a first-degree relative who had a good response to a particular stimulant, we recommend trying that stimulant medication first. Conversely, if the child had a poor response and/or problematic side effects with a stimulant or has a first-degree relative who did not respond well to a particular stimulant, we would suggest trying a different stimulant medication first.

Dextroamphetamine and Adderall, like methylphenidate, are safe medications with relatively few side effects and half-lives that are longer than that of methylphenidate, but still fairly short. Growth suppression with the amphetamine compounds may be greater than that with methylphenidate, but rebound growth after cessation of amphetamine compounds may also be greater (see Table 12 for a comparison of psychostimulant properties). Anorexia and weight loss caused by dextroamphetamine and Adderall may also be greater than with methylpheni-

TABLE 12 Comparison of Psychostimulants Properties

	Methylphenidate ^a	Dextroamphetamine/ Adderall	Pemoline
Sustained-release form	Yes	Yes	No (no need—half-life same as sustained-release methylphenidate and dextroamphetamine)
Anorexia	Less	Most	Less
Growth suppression	Less	Most	Less
Addictive potential	Less	Most	Least
Sympathomimetic arousal	Yes	Yes	Less
Can cause chemical hepatitis	No	No	Yes
Can cause increase in heart rate/blood pressure	Yes	Yes	Less

^a Side effects may be less with Concerta preparation of methylphenidate than with standard preparation of methylphenidate.

date. The amphetamines are believed to be the most potentially addictive of the psychostimulants, although when prescribed therapeutically, abuse/dependence has not been shown to occur (Barkley, 1990; Dulcan, 1990).

Dosing and Administration

The therapeutic dose range for dextroamphetamine and Adderall are one-half to two-thirds that of methylphenidate (i.e., 0.15–0.5 mg/kg/dose) (American Academy of Pediatrics, 1996; PDR, 2001). This translates into a starting dose of 2.5 mg of dextroamphetamine (half of the smallest dextroamphetamine capsule) after breakfast and lunch for children less than 30 kg and 5 mg after breakfast and lunch for children who weigh more than 30 kg. Adderall is started at 5 mg in the morning after breakfast for children who weigh less than 30 kg and 5 mg in the morning and 5 mg 4–6 hours later in children weighing more than 30 kg. Adderall should be increased by 5 mg increments weekly/every other week (PDR, 2001). It is particularly important to ensure that amphetamine compounds are given after meals whenever possible, since these medications are more anorectic than either methylphenidate or pemoline. Dose adjustment and assessment are similar to those prescribed for methylphenidate.

Adderall also has a longer half-life (8–12 hr) than dextroamphetamine, so that nearly 40% of ADHD patients are able to be treated satisfactorily with once-a-day dosing and over 50% can be maintained on twice-per-day dosing (Swanson et al., 1998). Only 7% of patients required dosing three or more times per day. This may facilitate compliance, particularly for children who find taking medication during school hours embarrassing. It should be noted, however, that recent investigation suggests that dextroamphetamine sulfate has comparable efficacy and slightly longer duration of action than Adderall (Gault et al., 1999; James et al., 2000).

Sustained/Extended-Release Methylphenidate and Dextroamphetamine

Regularly administered methylphenidate and dextroamphetamine typically require b.i.d. dosing, which often means that the child is administered a dose while in school. Often, school personnel, i.e., the school nurse, will administer the medication. This can obviously be a potential source of embarrassment for children and potentially lead to noncompliance and resistance to taking the medication (Firestone, 1982; Brown et al., 1985; Medical Letter, 1994). Sustained- and extended-release methylphenidate (Ritalin-SR and Metadate ER, respectively) and dextroamphetamine (Dexedrine spansules) can be effective for up to 8 hours and were developed, in part, to circumvent b.i.d. dosing regimens and potentially facilitate medication compliance (Findling and Dogin, 1998). It should be noted, however, that sustained-release preparations can take up to 3 hours to have any effect. Sustained-release methylphenidate (Ritalin-SR), available only in 20 mg

tablets, is, in theory, comparable to 10 mg methylphenidate after breakfast and 10 mg after lunch. This preparation can also be problematic in that it precludes using smaller doses (e.g., 10 mg) to titrate the dose.

While some controlled trials of sustained release preparations for methylphenidate and dextroamphetamine have reported that they are comparably effective to regular methylphenidate and pemoline (Whitehouse et al., 1980; Pelham et al., 1990; Fitzpatrick et al., 1992), some studies have suggested that regular methylphenidate is superior for individual children in almost every case (Brown et al., 1980; Pelham et al., 1987; Stevenson and Wolraich, 1989; Dulcan, 1990).

Sustained-release preparations of methylphenidate may not last as long as a second dose of regular methylphenidate. Increased day-to-day variability is also observed. A single daily dose of sustained-release methylphenidate is almost never adequate in ameliorating the target symptoms, so that once-daily dosing is rarely, if ever, successfully achieved. Tolerance to sustained-release methylphenidate after several months of therapy has been documented but has not been demonstrated when other stimulants are used therapeutically. A further disadvantage of sustained-release methylphenidate is that when it is chewed instead of swallowed, very high blood levels can result, with the whole dose being administered at the time it is taken with potentially severe toxic side effects (Rosse and Licamele, 1984). This may also be a problem with sustained-release dextroamphetamine spansules, so these should also not be chewed (Findling and Dogin, 1998).

In view of the aforementioned concerns with sustained-release preparations, we do not consider them to be particularly useful medication for the child psychopharmacologist. The advent of 2.5 mg, 5 mg, and 10 mg dexmethylphenidate HCL (focalin) and new extended-release preparations of methylphenidate (Metadate ER) may allow more flexibility in dosage titration resulting in better clinical responses. Wilens (2000) recently reported the safety and efficacy of Concerta (oros methylphenidate) extended-release tablets in 436 children 6–13 years of age treated with once-a-day Concerta for up to 12 months. Concerta is the only currently available preparation of methylphenidate that achieves a 12-hour duration of effect. The medication is FDA approved for the treatment of children with ADHD. The Alza Corporation markets Concerta and has recently reported significant improvement in distractibility attention and hyperactivity across three controlled studies in 416 patients with ADHD, 6–12 years of age. Use of Concerta also eliminates the need for administering doses during and after school. A single morning dose (18–54 mg/day) of Concerta is administered. Typical starting doses are 18 mg/day, and the medication can then be titrated to a maximum of 54 mg/day. There has also been the suggestion that Concerta may be more effective than standard methylphenidate with fewer side effects in some patients with ADHD. Further investigation is clearly warranted, particularly when the data is published in a refereed journal.

One dose daily Adderall XR (available in 10 mg, 20 mg, and 30 mg capsules) may also be an attractive alternative. Its time to peak concentration is approximately 7 hours and, therefore, 4 hours longer than immediate-release Adderall (Adderall XR package insert, Shire US Inc., 2001). Once-daily extended-release preparations (e.g., Concerta, Adderall XR) may offer considerable advantages in terms of facilitating medication compliance.

Pemoline

Pemoline is used far less commonly than the other stimulants. It can be useful, however, since it lacks significant sympathomimetic activity and is sometimes helpful when the other, more commonly used psychostimulants have caused intolerable side effects. It should be noted that when the stimulants have caused a psychosis or severe tic/movement disorder, pemoline should probably not be used. Enthusiasm for prescribing pemoline has also been dampened by its increased association with liver toxicity. Thus, many clinicians are loath to prescribe this medication at all and will use antidepressant medications (see Chapters 8 and 10) and α_2 -adrenergic agents (see Chapter 16) instead of pemoline if methylphenidate and amphetamine preparations are unsuccessful in treating ADHD.

Dosage and Administration

Pemoline has the advantage of usually being given one time per day. It is usually started at a dose of 37.5 mg in the morning and then increased gradually by 18.57 mg per week to 0.5–3 mg/kg day (PDR, 2001). When the child is obese and particularly large, an initial dose of 37.5 mg/day may be implemented. The maximum dose is 112.5 mg/day. Older adolescents will sometimes require higher doses. The lowest dose that effectively alleviates symptoms with minimal toxicity is targeted. Pelham et al. (1995) demonstrated that anti-ADHD effects of pemoline can last at least 7 hours. A single morning dose of pemoline (1–2 mg/kg) is typically sufficient for most patients with ADHD (Sallee et al., 1992; American Academy of Pediatrics, 1996).

In contrast to the other stimulants, pemoline does not cause an increase in heart rate or blood pressure, but it can cause a chemical hepatitis (Table 12) so that LFT monitoring is required when it is used.

Sallee and colleagues (1989) found that the acute initial administration of a single dose of pemoline 2 mg/kg resulted in a significant improvement in attention to task within 2–3 hours after the dose in 20 6- to 12-year-old children with ADHD. Of these children, 25% developed abnormal involuntary movements of the extremities, trunk, face, and mouth (Sallee et al., 1985, 1989). On repeated doses, however, these movements dissipated in all but one of the children. Increasing the dose of pemoline sooner than recommended may, however, expose

children to unpleasant and potentially debilitating side effects and cannot be recommended at this time.

Finally, recent investigation suggests a potential role for the novel selective noradrenergic enhancer and nonpsychostimulant, tomoxetine, in the treatment of ADHD. Spencer and colleagues (1998) conducted a double-blind, placebo-controlled crossover study of tomoxetine in 22 adults with ADHD. A striking improvement in ADHD symptoms was observed at a mean oral dose of 76 mg/day. Eleven of 21 patients treated with tomoxetine improved, whereas only 2 of 21 patients demonstrated clinical improvement while on placebo. Eli Lilly recently sponsored two multicenter double-blind, placebo-controlled studies of tomoxetine in pediatric ADHD. One hundred and forty-seven patients were studied, with 65 receiving tomoxetine, 62 placebo, and 20 methylphenidate (Heiligenstein et al., 2000). Patients were classified as stimulant-naïve versus stimulant-prior exposure and randomized to receive 9 weeks of double-blind treatment (methylphenidate, tomoxetine, or placebo). Tomoxetine was administered in divided doses before and after school and titrated to a maximum of 200 mg/day. In both studies, tomoxetine treatment resulted in greater clinical improvement in pediatric ADHD patients than placebo. Tomoxetine demonstrated comparable safety and efficacy, as did methylphenidate.

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8

Tricyclic Antidepressants

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In recent years, the selective serotonin-reuptake inhibitors (SSRIs) and newer novel antidepressants have become the first-line antidepressants used by most clinicians for adults because of their established efficacy, relatively benign side effects, and ease of administration (see Chapter 9). Tricyclic antidepressants (TCAs) are no longer considered first-line treatment despite their established efficacy in adults with major depressive disorder (MDD) (Glassman and Roose, 1990). While child and adolescent MDD appears to exhibit comparable SSRI responsiveness as adult MDD, there is no conclusive evidence that TCAs are superior to placebo in pediatric MDD (Ryan and Varma, 1998). In fact, noradrenergic and mixed noradrenergic/serotonergic TCAs do not appear to be effective at all in pediatric MDD. Nonetheless, investigation has revealed other potential roles for TCAs in the treatment of child and adolescent conditions, a topic that will be discussed in this chapter. We will also explore the present status of psychopharmacology in child and adolescent major depression and suggest possible future directions. The reader is also referred to the excellent and comprehensive review on TCA use in children and adolescents by Geller and colleagues (1999).

CHEMICAL PROPERTIES

The TCAs, such as imipramine, desipramine, clomipramine, amitriptyline, and nortriptyline, are dibenzapine derivatives (Table 1). Because they undergo significant first-pass metabolism by the liver and are less bound to proteins, these agents are metabolized significantly more rapidly in children and adolescents than in adults. This faster metabolism is true for all compounds with primary hepatic metabolism because of the greater liver mass in relation to body size in children and adolescents. Children and adolescents, like adults, can show a more than 30-fold difference in heterocyclic blood levels at a particular dose (Preskorn et al., 1983; Sjoquist and Bertilsson, 1984; Ryan et al., 1987a), and steady-state TCA levels can vary widely in children receiving fixed daily doses of medication (Preskorn et al., 1989). Liver biotransformation of TCAs primarily involves oxidation, aromatic hydroxylation, and demethylation. Approximately 5% of the population are "slow hydroxylators" and will have significantly longer half-lives and higher plasma blood levels (Potter et al., 1982). These are persons who metabolize TCAs slowly and may develop central nervous system (CNS) side effects which need to be differentiated from worsening of depression or attention-deficit hyperactivity disorder (ADHD) (Preskorn et al., 1989). Because severe cardiotoxicity and deaths have been reported (Preskorn et al., 1989), close monitoring of TCA blood levels is required.

The mechanism by which TCAs are effective in the treatment of adult MDD and other disorders has not been clearly established. There is, however, evidence that these agents affect monoamine neurotransmitter systems in the CNS, such as serotonin and norepinephrine (Arana and Hyman, 1991). The TCAs block the reuptake of norepinephrine and serotonin, potentiating their action. It has been

TABLE 1 Relative Neurotransmitter Effects of Tricyclic Antidepressants

	Noradrenergic	Serotonergic	Dopaminergic
Imipramine	++	++	0
Amitriptyline	++	++	0
Desipramine	+++	+/-	0
Nortriptyline	+++	+/-	0
Fluoxetine	0	+++	0
Trazodone	0	+	0
Maprotiline	+++	0	0
Bupropion	0	0	+++

Source: Ryan, 1990.

suggested that TCAs work by increasing noradrenergic and/or serotonergic transmission, compensating for a presumed deficiency (Arana and Hyman, 1991).

INDICATIONS

(See Table 2.)

Depression

Child and adolescent depression is now recognized as a valid diagnostic entity with several investigations corroborating its validity (Cytryn et al., 1972; Weinberg et al., 1973; Puig-Antich et al., 1978; Carlson and Cantwell, 1979; Strober et al., 1981; Orvaschel et al., 1982; Kovacs et al., 1984a; Chambers et al., 1985; Ryan et al., 1987b). Child and adolescent depression has also been demonstrated to be continuous with adult depression (Ryan et al., 1992a, 1994; Rao et al., 1995, 1996; Williamson et al., 1995; Birmaher et al., 1996a, 1996b). This continuity includes clinical phenomenology and course as well as associated neurobiology. As in adults, controlled trials have demonstrated that psychotherapy is effective in children and adolescents with MDD (Lewinsohn et al., 1994; Brent et al., 1997; Birmaher et al., 1996a, 1996b; Hoberman et al., 1996; Reinecke et al., 1998). This continuity of pediatric and adult depression is consistent with pediatric depression representing the same condition as adult depression (Kovacs et al., 1984b; Ryan et al., 1987b; Puig-Antich et al., 1989).

Symptom Frequency and Severity

Ryan and colleagues (1987b) compared symptom frequency and severity in two sequential samples of 95 prepubertal children and 92 adolescents, aged 6–18 years, all assessed according to the Schedule for Affective Disorders and Schizo-

TABLE 2 Clinical Indications for TCAs

FDA-approved indications:

Enuresis

Established indications:

Enuresis

ADHD in children and adolescents

Probable indications:

ADHD in adults

School absenteeism/school phobia

OCD (Clomipramine only)

Depression

phrenia for School-Aged Children (Ryan et al., 1987b). All met research diagnostic criteria (RDC) for MDD. No significant differences between the two groups in the majority of depressive symptoms were noted. Adolescents were, however, observed to have greater anhedonia, hopelessness, hypersomnia, weight change, drug and alcohol use, and lethality of suicide attempt, whereas prepubertal children had more depressed appearance, somatic complaints, agitation, separation anxiety, phobias, and hallucinations. Children and adolescents whose depression had lasted at least 2 years had significantly higher rates of suicide attempts, ideation, and lethality than those with depressions of shorter duration (Table 3).

Endogenous and Anxious Factors in Depression

Ryan and colleagues (1987b) also studied a discrete population of 296 children who met DSM-III criteria for diagnoses for any axis I psychiatric disorder. As has been found in many adult depression studies, factor analysis revealed both an "endogenous" and an "anxious" factor (Table 4) (Nelson and Charney, 1981; Young, 1983; Young et al., 1986). Ryan and associates (1987b) also observed three other factors: negative life conditions, appetite and weight changes, and conduct disturbance. They concluded that relatively few differences are seen between children and adolescents with MDD, and these differences are overshadowed by their similarities (Nelson and Charney, 1981; Young, 1983; Young et al., 1986).

TABLE 3 Prepubertal Versus Adolescent Depression

Depressive signs and symptoms	Prepubertal children	Adolescent
Anhedonia	Less	More
Hopelessness	Less	More
Sleep	Hyposomnia	Hypersomnia
Weight	Less likely to change	Often changes
Suicide	Decreased lethality of attempt	Increased lethality of attempt
Appearance	More depressed	Less depressed
Somatic complaints	More	Less
Separation anxiety, phobias, hallucinations	More	Less

Source: Rosenberg et al., 1992.

TABLE 4 Factors Associated with Child and Adolescent Depression

Endogenous
Anxious
Negative life conditions
Appetite and weight changes
Conduct disturbance

Source: Rosenberg et al., 1992.

Family History

As reported by Puig-Antich and colleagues (1978), a family history of mood disorders in parents is associated with a much greater likelihood of a mood disorder in their children. This, in turn is associated with an increase in the lifetime risk for mood disorders (Hagrell et al., 1982; Robins et al., 1984; Joyce et al., 1990; Ryan et al., 1992b). It has been estimated that at any one time as many as 1 in 20 children and adolescents have MDD (Lewinsohn et al., 1986, 1993, 1994; Anderson et al., 1987, 1989; Kashani et al., 1987a, 1987b; Fleming et al., 1993). Recent investigation has found that children with parents with MDD are approximately three times more likely to have an episode of MDD (Birmaher et al., 1996a, 1996b). In fact, in children of parents with MDD, the lifetime risk for MDD ranges from 15% to 45% (Orvaschel et al., 1988; Hammen et al., 1990). Merikangas et al. (1988) also demonstrated a significant increase in the lifetime risk for suffering from an episode of MDD when both parents suffer from mood disorders. Conversely, first-degree relatives of children and adolescents with MDD have lifetime prevalence rates of MDD ranging from 20% to 46% (Strober, 1984; Livingston et al., 1985; Mitchell et al., 1989; Kutcher and Marton, 1991; Todd et al., 1993; Williamson et al., 1995). This is also consistent with familial studies in adults with MDD, which have demonstrated lifetime rates of depressive disorders in their relatives to be two- to three times higher as compared to healthy controls (Gershon et al., 1982; Weissman et al., 1982, 1984a, 1984b; Tsuang et al., 1985). The more family members with depression, the younger the age of onset of MDD (Weissman et al., 1984b, 1988; Puig-Antich et al., 1989). Recent investigation using brain imaging has found brain abnormalities in the prefrontal cortex, caudate nucleus, and amygdala to be more prominent in adults with familial MDD (patients with at least one first-degree relative with either MDD or bipolar disorder) than in nonfamilial MDD patients (patients without any first-degree relative with MDD or bipolar disorder) and healthy controls (Drevets et al., 1997; Ongur et al., 1998). This has been recently extended to children with

distinct neuroanatomic and neurochemical alterations observed in pediatric patients with familial MDD as compared to pediatric patients with nonfamilial MDD (Nolan et al., In press; Farcheone et al., In press). Recently born individuals have a greater probability than their grandparents of developing a mood disorder. Both longitudinal and cross-sectional studies using population and family study samples have demonstrated an increased prevalence of mood disorders in adults (Puig-Antich, 1987b).

Biological Abnormalities

Biological abnormalities have been identified in children with depression (Table 5). Puig-Antich (1987b) reported increased growth hormone (GH) secretion during sleep in depressed children. These children also secrete less GH in response to insulin-induced hypoglycemia. This abnormality persists after resolution of the depression and cessation of the pharmacological intervention. This is an important finding since identification of this GH abnormality could serve as a marker of depression even after the depression has resolved (Puig-Antich, 1987; Synopsis of Psychiatry, 1988; Weller and Weller, 1990).

Kutcher and associates (1988) observed increased nocturnal GH secretion at midnight and 1:00 a.m. in nine depressed adolescents, as compared with nine normal controls. Another study examining unstimulated GH secretion in adolescents found blunted nocturnal GH in those depressed adolescents who were suicidal, as compared with normal controls (Dahl et al., 1992). Ryan and associates (1988) have shown blunted GH response to desmethylimipramine in depressed suicidal adolescents as compared with normal controls, but not in depressed non-suicidal adolescents. Jensen and Garfinkel (1990) did not show differences in GH response to oral clonidine or L-dopa in adolescent boys, but the number of subjects in the study was small (eight MDD versus five normals). Meyer and associates (1991) found significantly lower 24-hour mean GH concentration in depressed boys than in normal boys, and significant blunting was found in both the 8:00 a.m. to 8:00 p.m. period and the 8:00 p.m. to 8:00 a.m. period. Ryan and colleagues failed to demonstrate any difference in nocturnal GH secretion between prepubertal MDD and normal control children so that abnormalities of

TABLE 5 Biological Abnormalities in Child and Adolescent Depression

<i>Increased</i> GH secretion during sleep
Secrete <i>less</i> GH in response to insulin-induced hypoglycemia
50% <i>do not</i> suppress cortisol when given DST
EEG <i>not</i> helpful

Source: Rosenberg et al., 1992.

unstimulated GH secretion in depressed children and adolescents appears to be complicated by maturational changes, and its interpretation remains unclear (Ryan and Dahl, 1993).

Other measurements of biological abnormalities in children and adolescents with MDD include the dexamethasone suppression test (DST) and sleep electroencephalography. As with GH secretion, some findings are similar to those found in adults, but there do appear to be some major age-related differences.

Abnormal DST

Studies which adjusted for age, weight, and faster rate of metabolism in children reveal that 50% of depressed children and adolescents do not suppress cortisol upon being given the DST (Casta et al., 1989; Weller and Weller, 1990). Weller and associates (1986) showed that children who do not suppress cortisol secretion after the DST are at higher risk for relapse of their mood disorder. Birmaher and colleagues (1992), however, reported a study of 24-hour serial cortisol determinations measured during baseline and after the administration of 0.25 and 0.5 mg of dexamethasone in a sample of outpatient children with MDD, nonaffective psychiatric controls, and normal controls. The 24-hour baseline cortisol measurement and the DST did not distinguish among the three groups. The investigators measured 24-hour serum dexamethasone levels; no significant group differences were observed. These results raised serious questions as to the usefulness of this test in the diagnosis of mood disorders in children (Birmaher et al., 1992).

Electroencephalography

Unlike adults, sleep electroencephalography has not proved helpful in delineating childhood and adolescent depression.

Neuroimaging

Functional neuroimaging studies in adult MDD patients have demonstrated decreased metabolic rates in the caudate nucleus associated with severity of illness and treatment response (Baxter et al., 1985, 1989; Buchsbaum et al., 1986; Baxter, 1991). More recent investigation of brain chemistry with proton magnetic resonance spectroscopy (1-H MRS) has demonstrated abnormalities in choline-containing compounds in prefrontal-striatal and hippocampal brain regions (Charles et al., 1994; Renshaw et al., 1997; Ende et al., 1997; Sonawalla et al., 1999). This finding has been extended to depressed children and adolescents (Farchione et al., in press; Steingard et al., 2001). Abnormalities in choline-containing compounds may also serve as a potential marker of response to antidepressant treatment. Charles et al. (1994) found that basal ganglia choline-containing compounds in adult MDD patients decreased to normal levels after antidepressant treatment. Abnormalities in choline compounds in the basal ganglia of MDD patients have also been shown to be most pronounced in antidepressant treatment

TABLE 6 Tricyclic Antidepressant Pharmacotherapy of Depression in Different Age Groups

Age group	Effectiveness
Child	Ineffective
Adolescent	Ineffective
Middle aged	Very effective
Elderly	Appears to be effective

Source: Adapted from Rosenberg et al., 1992.

responders (Renshaw et al., 1997), suggesting that pretreatment choline levels in the basal ganglia may represent a marker for drug response (Sonawalla et al., 1999). Ende et al. (1997) have identified hippocampal abnormalities in choline levels in adult MDD patients that normalize after electroconvulsive therapy (ECT). The increased prefrontal cortical choline levels appeared to be most prominent in pediatric patients with at least one first degree relative with MDD (Farchione et al., In press; Dr. Perry Renshaw, personal communication). Further study of the potential role of choline-containing compounds in pediatric MDD patients is clearly indicated to determine its role in helping predict response to treatment (or lack thereof).

Indications for Pharmacotherapy

See Table 6.

Major Depressive Disorder

Controlled studies have failed to demonstrate that TCAs are superior to placebo in the treatment of childhood and adolescent MDD (Kramer and Feiguine, 1981; Petti and Law, 1982; Kashani et al., 1984; Preskorn et al., 1987; Puig-Antich et al., 1987; Geller et al., 1989, 1990; Hughes et al., 1990; Klein et al., 1992, 1998; Kutcher et al., 1994; Ryan and Varma, 1998; Birmaher et al., 1998; Kye et al., 1996). While methodology in the aforementioned studies was sound, many of the studies consisted of small sample sizes. Hazell et al. (1995) conducted a meta-analysis that demonstrated that TCAs were not superior to placebo in child and adolescent MDD. SmithKline Beecham recently conducted a multicenter randomized controlled study of pediatric MDD comparing 270 patients treated with paroxetine, imipramine, or placebo (Ryan and Varma, 1998; SmithKline Beecham, data on file, December 1998). Paroxetine was found to be superior to both imipramine and placebo, while imipramine was not significantly better than placebo. Thus, noradrenergic and serotonergic/noradrenergic antidepressants do not appear to be effective in child and adolescent MDD (Ryan and Varma, 1998).

It is not clear when the age shift occurs when young adults begin to respond to TCAs. This maturational difference in response has led to various hypotheses as to what might account for this age shift in responsiveness to TCAs. We do know that estrogen effects peak in adolescence and that alterations in the noradrenergic system are particularly prominent during this time.

Study of nonhuman primate models can also be instructive. For example, genetic and psychosocial stressors that increase the risk for depression also affect noradrenergic and serotonergic functioning (Rosenblum et al., 1994; Clarke et al., 1995; Coplan et al., 1996). Serotonergic systems have been shown to mature earlier than dopaminergic and noradrenergic systems (Goldman-Rakic and Brown, 1982; Rosenberg and Lewis, 1994, 1995). It has been suggested that the earlier maturation of serotonergic systems and the later maturation of noradrenergic systems allow for effective intervention with SSRIs in child and adolescent MDD but preclude intervention with noradrenergic and mixed serotonergic/noradrenergic TCAs (Ryan and Varma, 1998).

Additional possible reasons for the lack of documented efficacy of TCAs in child and adolescent MDD include the patients studied representing a particularly severe, chronic, and refractory subtype of illness (Geller et al., 1992). MDD in childhood also carries an increased risk for bipolar disorder, and predicting those who will ultimately be diagnosed with bipolar disorder remains problematic. The placebo response rate in pediatric patients with MDD is quite high even with placebo “washouts,” and adequate explanation has proved elusive (Birmaher et al., 1998).

Intravenous Clomipramine

Because oral TCA administration has not been shown to be effective in child and adolescent MDD, alternative approaches have been investigated. Sallee and colleagues (1997) treated 16 nonsuicidal adolescents with MDD in a randomized controlled trial with a single intravenous 200 mg dose of clomipramine and placebo. They observed significant improvement in depressive symptoms 6 days after treatment but no improvement after 3 days of treatment. Intravenous clomipramine administration in MDD adolescents resulted in an 88% response rate compared to a 38% response rate in patients receiving placebo. Seven patients treated with IV clomipramine demonstrated a decrease in their depressive symptoms over 50%, while only three patients treated with placebo exhibited comparable improvement. Perhaps most striking of all was the rapidity of response, which contrasts with the typical delayed response of oral antidepressant treatment. Further study is clearly warranted.

Electroconvulsive Therapy

While ECT has not been systematically studied in child and adolescent MDD, in adults it remains the most potent treatment for MDD and is often used as the treatment of choice after a failure of antidepressant therapy (Kendell, 1981;

Crowe, 1984; Fink, 1985; Zorumski et al., 1986). ECT has been shown to be safe, and its side-effect profile compares quite favorably with that of the antidepressants. Recent investigation suggests that ECT may also be effective in refractory adolescents, although clear evidence establishing the efficacy and specific indications for this treatment modality in child and adolescent MDD is lacking.

Current Practice

Because the TCAs have not been demonstrated to be superior to placebo and given their side effect profile and potential for toxicity in overdose, we do not recommend their use for child and adolescent MDD. Given the safety profile and recent data suggesting the efficacy of the SSRIs in child and adolescent MDD (see Chapter 9), these medications are now first-line treatment. In fact, the TCAs cannot be considered the first drug of choice for any psychiatric condition, particularly in view of the outstanding issues of increased risk for arrhythmias and sudden cardiac death (discussed in detail under Contraindications and Side Effects) (Geller et al., 1999).

We believe that the risks of TCA trials outweigh their potential benefits in children and adolescents with MDD. Moreover, newer novel antidepressants (e.g., bupropion, mirtazapine, nefazadone, venlafaxine, etc.) have been developed (see Chapter 9) which have a more benign side effect profile than the TCAs.

Psychotherapy has also been demonstrated to be effective in child and adolescent MDD and should be included in treatment planning. Antidepressant treatment is best commenced when psychotherapy is either ineffective or inadequate given the severity of the condition. Alternative approaches including intravenous clomipramine also merit further study, although this is not readily available in clinical settings.

Attention-Deficit Hyperactivity Disorder

Up to 30% of children treated with stimulants for ADHD do not improve, necessitating alternative treatments (Barkley, 1977; Rapoport and Zametkin, 1980). Imipramine, desipramine, amitriptyline, and clomipramine have been shown to be superior to placebo in the treatment of ADHD (Garfinkel et al., 1983; Donnelly et al., 1986; Gittelman-Klein, 1987; Biederman et al., 1989b). It should be noted that although these studies have demonstrated the antidepressants to be more effective than placebo, most studies find stimulants to be superior to antidepressants (Rapoport et al., 1974; Rapoport and Mikelson, 1978; Campbell et al., 1985). One contrary report (Werry et al., 1979) found imipramine to be more effective than placebo in treating children with ADHD, while both methylphenidate and imipramine were more effective than placebo. Wender (1988) has observed that when used to treat ADHD, TCAs improve mood and hyperactivity, but they do not improve concentration, and they may be sedating.

In a double-blind, placebo-controlled crossover study of 12 prepubertal male children with ADHD comparing the efficacy of methylphenidate, desipramine, and clomipramine, it was seen that while methylphenidate was significantly better than desipramine and clomipramine in improving classroom functioning, clomipramine was more effective than imipramine in decreasing aggressive, impulsive, and depressive/mood symptoms (Garfinkel et al., 1983). Further study of clomipramine in treating children and adolescents with ADHD is clearly warranted. Desipramine is still considered the first-line TCA to treat ADHD because it is the most studied of the antidepressants. It also has a relatively favorable anticholinergic and sedating side-effect profile as compared with other TCAs, including clomipramine. It is likely, however, that any TCA would be similarly effective in the treatment of ADHD (Ryan, 1990). It is important to point out that the long-term (i.e., more than a few months) efficacy of the TCAs has not been established.

In a double-blind controlled study comparing the efficacy of the psychostimulant dextroamphetamine, the TCA imipramine, and placebo in reducing ADHD behaviors, Winsberg and colleagues (1972) reported that both dextroamphetamine and imipramine were significantly more effective than placebo. While Rapoport and associates (1974) found both imipramine and methylphenidate to be superior to placebo in boys with ADHD, one-year follow-up suggested reduced effectiveness with more hostility in patients treated with imipramine (Quinn and Rapoport, 1975). Yepes et al. (1977) found that both the TCA amitriptyline and the psychostimulant methylphenidate were more effective than placebo in reducing ADHD behaviors during a 2-week investigation. Consistent with Quinn and Rapoport's (1975) report of decreased effectiveness of maintenance imipramine treatment at 1-year follow-up, Yepes and colleagues (1977) also noted the possibility of tolerance to amitriptyline during maintenance/long-term treatment.

Donnelly et al. (1986) noted significant behavioral improvement in children with ADHD treated for 2 weeks with desipramine and found that clinical improvement was associated with a reduction in 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine. Biederman and colleagues (1989b) also found desipramine to be superior to placebo in 62 children with attention-deficit disorder including children who had not responded to psychostimulant intervention.

Typically, TCAs or bupropion (see Chapter 9) are tried after the failure of at least two stimulant trials (Pliszka et al., 2000) (Table 7). There are no data to suggest that the TCAs are more or less effective than bupropion in the treatment of ADHD.

There are no guidelines as to how long to maintain ADHD patients on TCAs. With recent investigation showing that adults continue to exhibit ADHD symptoms and can benefit from stimulant medication (see Chapter 3), we recommend using the same principles for medication management described for treating

TABLE 7 Dosage and Regimen of TCAs Used in the Treatment of Major Depressive Disorder***Imipramine:**

Used at doses up to 5.0 mg/kg/day.

Preskorn et al.: among children responders, serum levels of 125–250 ng/mL.

Puig-Antich et al.: serum levels in children >150 ng/mL optional.

Start with dose 75 mg/day.

After 7–10 days draw serum desipramine and imipramine levels.

Formula: new dose = (initial dose/initial plasma level) × desired level.

Adolescents: no significant relationship between serum level and clinical response.

Generally raised to serum levels >150 ng/mL (adult levels).

Careful monitoring required.

Desipramine:

Used at doses up to 5 mg/kg/day.

No evidence of relationship between plasma level to clinical response.

Children and adolescents treated with serum levels effective in adult MDD.

Usually increased to achieve serum levels >150 ng/mL as in adults.

Serum levels >150 ng/mL may increase risk for ECG abnormalities (i.e., increased heart rate, conduction abnormalities) (may be of more statistical than clinical significance).

Careful monitoring required.

Nortriptyline:

Titrated to give serum levels between 75–100 mg/mL.

Usually requires daily doses of 0.5–2.0 mg/kg.

Careful monitoring required.

Amitriptyline:

Typically used at doses up to 5.0 mg/kg/day.

Serum levels not useful in monitoring efficacy or toxicity.

Careful monitoring required.

High anticholinergic and sedating side effects make problematic.

Clomipramine:

No standardized guidelines.

Dugas et al.: open trial doses 0.24–2.93 mg/kg/day effective in 12/26 children and adolescents with “depressive” symptoms.

Double-blind, placebo-controlled studies needed.

Relatively unfavorable side-effect profile.

Careful monitoring required.

Doxepin:

Available in oral solution.

More water-soluble (free of alcohol) than nortriptyline.

Not studied in children and adolescents.

Unfavorable side-effect profile.

Maprotilene:

Antidepressant most associated with seizure induction.

* TCAs have not been demonstrated to be superior to placebos in child and adolescent major depressive disorder and because of their side effect profile, we do not recommend their use for child and adolescent depression.

ADHD children and adolescents with stimulants. Frequent assessment of the need for medication is warranted. Trials off medication (e.g., over the summer, holidays) may also be helpful, although tapering is necessary particularly when higher doses of the TCAs are used. Finally, placebo-controlled, double-blind studies may help to determine whether or not the medication is truly benefiting the child. Standard regimens can be found in Table 8.

ADHD in Adults

Until recently, many practicing clinicians believed that ADHD remitted at puberty, but further investigation has shown that its course is extremely variable and that symptoms can persist into adolescence and adulthood (Wender, 1987). Stimulants have been found to be effective in treating ADHD symptoms throughout life. This is an area worthy of investigation. Adult patients with ADHD who fail to respond to stimulant medication may benefit from a TCA trial (e.g., desipramine) or bupropion. Comorbid diagnoses of depression are also not uncommon in patients with ADHD. The tricyclic antidepressants and bupropion have demonstrated efficacy in adults with MDD.

ADHD and Coexisting Tics

The existence of tic symptoms may warrant a TCA trial. These agents have the advantage that they are effective in the treatment of ADHD but do not typically exacerbate tics. For a full discussion of stimulant-induced tics and how to manage patients with a personal or family history of tic disorders, refer to Chapters 7 and 16.

We recommend using desipramine as the first TCA in the treatment of ADHD and tics. This antidepressant has a relatively favorable side effect profile, and there is some literature to support its use (Riddle et al., 1988). It should be noted that it is not an effective treatment of tic disorders. Singer et al. (1995) compared clonidine versus desipramine versus placebo in children with ADHD and comorbid Tourette's syndrome. Desipramine, clonidine, and placebo were administered randomly with 1-week washout periods in between treatment change. Desipramine was more effective than both clonidine and placebo in improving problematic behavior, while none of the conditions resulted in worsening of tics. More recent investigations (Gadow et al., 1995; Castellanos et al., 1997) have suggested that stimulants may be safely prescribed in some children with ADHD and comorbid tic disorders (see Chapter 7). In view of potential cardiac risks, including sudden cardiac death in children treated with desipramine, caution and very close monitoring is indicated when desipramine is prescribed (see Contraindications and Side effects, below).

We recommend a trial of desipramine in a child or adolescent who develops tics or whose worsening of tic behaviors when treated with stimulants and whose

TABLE 8 Dosage and Regimen of TCAs for ADHD**Desipramine:**

Optimal dose 2.5–5 mg/kg/day.

Should not exceed serum levels >300 ng/mL.

No significant correlation between serum level, dosage, and clinical response.

Serum levels >150 ng/mL and doses >3.5 mg/kg/day associated with increased risk of heart rate increase and altered cardiac conduction.

Serum levels <300 ng/mL, ECK PR < 200 ms and QRS < 120 ms advocated.

Daily doses >5 mg/kg/day may be needed clinically to achieve serum levels >150 ng/mL.

Doses >3.5 mg/kg may be too much for some children.

Careful monitoring required.

Heterocyclic of choice.

Imipramine:

More effective than placebo.

Less effective than stimulants.

Used when desipramine is ineffective and/or if patient has difficulty falling or staying asleep.

Dosing and administration guidelines similar to desipramine.

More anticholinergic and sedating side effects than desipramine.

Careful monitoring required.

Nortriptyline:

Has not been systematically studied.

Anecdotal reports of efficacy.

Favorable anticholinergic and sedative side-effect profile.

May be considered if imipramine, desipramine, other “more standard” agents unsuccessful or contraindicated.

Careful monitoring required.

Amitriptyline:

Has not been systematically studied.

Unfavorable anticholinergic and sedative side-effect profile.

Not recommended for use.

Clomipramine:

Shown to be less effective than methylphenidate in improving overall classroom functioning.

More effective than desipramine in reducing scores reflecting aggressiveness.

More anticholinergic and sedative side effects than desipramine.

Less studied than desipramine.

Careful monitoring required.

Doxepin:

Not recommended for use in children and adolescents.

Maprotilene:

Not recommended for use in children and adolescents.

ADHD necessitates pharmacological treatment. It is important to emphasize, however, that if tics do not dissipate to a tolerable level after stimulant medication is discontinued, alternative therapy may be necessary with α -adrenergic agents such as guanfacine (Tenex) or clonidine (Catapres) (see Chapter 16), which can be effective in ameliorating both ADHD and tic symptoms. Further study is necessary to determine whether or not desipramine or other TCAs are safe and effective in treating ADHD with coexistent tics.

Enuresis

Enuresis remains the only FDA-established indication for the use of TCAs in children and adolescents. Their efficacy in treating this disorder have been demonstrated in over 40 double-blind studies (Ryan, 1990). Patients may become tolerant to the antienuretic effect, and it may wear off after several weeks. Many patients relapse once the medication is withdrawn. It should also be noted, however, that unlike TCA therapy of other psychiatric conditions, the antienuretic effect is seen without delay once treatment is initiated. Desipramine and imipramine, which are equally efficacious (Ryan, 1990), are the only antidepressants that have been approved by the FDA for the treatment of enuresis. Imipramine has more side effects (sedating and anticholinergic) but is less expensive (Ryan, 1990). Rapoport and colleagues (1978, 1980) found a significant association between imipramine plasma drug levels and antienuretic effect in some patients. It should be noted that some patients showed no antienuretic effect even with high plasma imipramine levels. It is recommended that desipramine be reserved for patients who have both diurnal and nocturnal enuresis or for those whose nocturnal enuresis has not responded to conservative behavioral measures or 1-deamino-8-d-arginine-vasopressin (DDAVP) (see below) (Rapoport et al., 1980).

Clomipramine has also been used to treat enuresis, with a therapeutic effect observed at plasma concentrations of 20–60 ng/mL (Dugas et al., 1980; Morselli et al., 1983). It must be emphasized that these pharmacological approaches should not be employed until organic etiologies are ruled out by physical and laboratory examination. Moreover, behavioral therapy (such as the bell-and-pad apparatus) is the treatment of choice for nonorganic functional enuresis. The TCAs are used as a supplement or when the child is away overnight or when DDAVP is ineffective or contraindicated. Children may become tolerant to these medications after approximately 6 months, and discontinuation of TCA therapy often results in symptom recurrence. These agents are recommended only after all other behavioral approaches and DDAVP treatment have failed and are likely to be effective only for short-term use. Standard dosing regimens can be found in Table 9.

TABLE 9 Dosage and Regimen of TCAs for Enuresis

Desipramine:

Equally effective as imipramine.
Typical doses 1–2.5 mg/kg/day.
Doses of 50–75 mg/day usually sufficient.
Antienuretic effects occur soon after treatment initiated.
Relationship of serum level to clinical outcome not clear.
Routine clinical practice: ECGs not usually done since final daily dose, usually ≤ 2.5 mg/kg/day.
Risk of cardiotoxicity low at these doses.
We recommend baseline ECGs, blood pressure/pulse checks, and serial ECG rhythm strips with blood pressure/pulse checks after each dose increase with recent reports of sudden cardiac death.

Imipramine:

Similar dosing and administration guidelines as for desipramine.
Titrated to give serum levels imipramine plus desipramine >60 ng/mL.
Desipramine preferred because of more favorable side-effect profile.
Has same antienuretic effects as desipramine.
Antienuretic effect not related to anticholinergic mechanism.
We recommend baseline ECGs, blood pressure/pulse checks, and serial ECG rhythm strips after each dose increase with recent reports of sudden cardiac death.

Nortriptyline:

Has not been studied.
Does not have FDA approval.
Not recommended for use.

Amitriptyline:

Has not been studied.
Unfavorable anticholinergic and sedative side-effect profile.
Not recommended for use.

Clomipramine:

Shown to be effective.
Targeted plasma concentration: 20–60 ng/mL.
Use only if desipramine and imipramine ineffective.
Side-effect profile less favorable than desipramine.
Plasma levels <20 ng/mL and >60 ng/mL associated with lack of efficacy.
We recommend baseline ECGs, blood pressure/pulse checks, and serial ECGs after each dose increase.

Doxepin:

Has not been studied.
Not recommended for use.

Maprotilene:

Has not been studied.
Not recommended for use.

Case History*

Alex, a 12-year-old boy, was referred for an evaluation of his learning disability and possible attention-deficit disorder. At the time of his evaluation, there was marked marital discord between the parents, indicating that separation was imminent, which would eventually end in divorce. Alex was very large for his age, very awkward, and poorly coordinated. He exhibited many specific learning disabilities affecting reading comprehension, auditory decoding, and penmanship. His poor fine-motor control contributed to an almost illegible handwriting. Printed words were also very difficult to identify because of reversals, indicating severe visuomotor integration problems.

During the course of the history taking, his mother indicated that Alex had always been severely enuretic, never having achieved nighttime bladder control for longer than 6 months. There were two 6-month periods, when he was 8 and 10 years old, respectively, when he was substantially continent. But even during these periods, he would be incontinent three to four times each month. Since the age of 5, he had had complete bladder control during the daytime. There were no episodes of soiling reported.

On examination, Alex appeared as a 12-year-old boy who looked somewhat older, primarily because of his obesity. There were no positive findings on the standard mental status examination. He appeared mildly dysphoric and had very low self-esteem. He did not meet any other criteria for an affective disorder. He related that he was overly active, distractible, impulsive, and restless. He also had a number of temper outbursts each week. He indicated that all forms of help, including alarms, changing in drinking habits, and parental awakenings in the first few hours of sleep, were ineffective.

Alex started on 50 mg of imipramine at bedtime and required an eventual dose of 200 mg before there was a moderate cessation of his enuresis. Wet nights decreased from nightly to three to four times per month. His parents agreed that they did not want any further treatment for the enuresis, since they felt that this was a sufficient improvement. They also noted good improvement in Alex's behavior, as well as a positive change in his affect and self-esteem.

Pediatricians not uncommonly use DDAVP as the medication treatment of first choice in enuretic children; TCAs tend to be used less frequently.

School Absenteeism/School Phobia/Separation Anxiety

Gittelman-Klein and Klein (1971) showed a superiority of imipramine over placebo in combination with a psychosocial treatment program after 6 weeks in 20 children and adolescents aged 7–15 years with anxiety-related school absenteeism. School attendance and anxiety improved significantly in patients on imipra-

* From Garfinkel, 1990.

mine compared to placebo. This finding has not been confirmed in other studies (Klein et al, 1992). Klein and colleagues (1980) suggest that imipramine can be effective in ameliorating separation anxiety, but that anticipatory anxiety often continues to be problematic. They observed that doses of 75–200 mg/day were effective for school-phobic children and adolescents, whereas patients with severe separation anxiety without school phobia sometimes responded to doses of 25–50 mg/day. School-phobic children and adolescents who responded to imipramine showed at least minimal improvement when doses of 125 mg/day were achieved. When clinical improvement occurred, further dose increments usually resulted in increased improvement (Klein et al., 1980). Maximal response most often was seen within 6–8 weeks. Klein and colleagues (1980) recommended continuing the effective imipramine dose for at least 8 weeks after symptom remission, and then gradually tapering and withdrawing the medication. Bernstein et al. (1990) compared imipramine to alprazolam to placebo in the treatment of school refusal. Many of the subjects had comorbid anxiety and depressive disorders. Neither imipramine nor alprazolam was found to be superior to placebo. Berney et al. (1981), using low-dose clomipramine, showed no superiority of medication over placebo in children with school phobia.

Klein and colleagues (1992) subsequently assessed the efficacy of imipramine as compared to placebo in children and adolescents with separation anxiety disorder. They were treated for a month with behavioral therapy. If they did not respond, they entered a double-blind, randomized, 6-week trial of imipramine or placebo. Of 45 patients accepted, 21 (47%) entered the trial. Approximately half of the children improved with either treatment, and imipramine revealed no superiority over placebo.

Bernstein and colleagues (2000a) recently assessed the efficacy of imipramine versus placebo in combination with cognitive-behavioral therapy in the treatment of school refusal. The investigation consisted of a randomized double-blind trial. Of 63 patients accepted, 47 (75%) completed the study. Significant improvement in school attendance was observed in the imipramine group but not in the placebo group. Seventy-five percent school attendance was considered to represent treatment remission. Of patients treated with imipramine, 54.2% met criteria for remission compared to only 16.2% of patients treated with placebo. The investigators also noted a significant reduction in anxiety and depression in patients treated with imipramine and placebo. Therefore, imipramine in combination with cognitive behavioral therapy was significantly more effective than placebo with cognitive behavioral therapy in treating school refusal in adolescents and in reducing depression in these patients.

Bernstein and colleagues (2000b) also measured compliance and side effects in the aforementioned investigation. As expected, patients treated with imipramine exhibited more side effects than patients treated with placebo. However,

there was no association between side effects and noncompliance or not continuing to participate in the study. Comorbid oppositional defiant disorder and increased family dysfunction were, however, significantly correlated with noncompliance with imipramine. When patients, mothers, and the psychiatrists were asked to guess medication or placebo condition, 66% of patients correctly guessed their assignment, 62.5% of mothers correctly guessed treatment cell, and 79.5% of psychiatrists correctly guessed treatment condition. Based on these findings, the authors recommended use of independent raters to monitor symptom changes during medication treatment trials.

Anxiety/Panic Disorder/Phobic Disorders

Ballenger and associates (1989) reported that three children with panic disorder and severe separation anxiety disorder and agoraphobia improved while receiving imipramine. It should be noted, however, that these children were also being treated with the anxiolytic alprazolam. Data are very limited on the treatment of panic disorder, phobic disorders, and anxiety disorders in children and adolescents. There have been no published placebo-controlled studies.

Obsessive-Compulsive Disorder

Clomipramine is an antiobsessional drug that has been found to be effective in the treatment of adult obsessive-compulsive disorder (OCD), and it has also been FDA-approved for the treatment of child and adolescent OCD. Clomipramine inhibits serotonin reuptake, thereby potentiating its effects, and its primary metabolite, desmethylclomipramine, inhibits norepinephrine reuptake (Davis and Glassman, 1991). Blocking serotonin reuptake is believed to be crucial to its anti-obsessive-compulsive actions. Clomipramine was previously believed to be more effective than the pure SSRIs such as fluvoxamine, fluoxetine, paroxetine, and sertraline. However, double-blind, placebo-controlled comparisons of the SSRIs vs. clomipramine in adult OCD patients have revealed comparable efficacy with more side effects in patients treated with clomipramine. There have been no such comparative trials in pediatric OCD patients.

Investigation in pediatric OCD patients have revealed high pretreatment levels of platelet serotonin to be a positive predictor of favorable clinical response to clomipramine therapy, which also results in a substantial reduction in platelet serotonin concentration (Flament et al., 1985). In a double-blind, placebo-controlled study of 19 OCD children and adolescents 10–18 years of age, clomipramine was shown to be superior to placebo. This antiobsessional effects appears to be distinct, at daily doses of 100–200 mg/day, from the antidepressant effect (Flament et al., 1985). In a follow-up study, Flament and associates (1987) showed the continued superiority of clomipramine over placebo.

Clomipramine has been shown to be superior to other TCAs in the treatment of OCD. In a 10-week crossover design, Leonard and colleagues (1989) found clomipramine to be superior to desipramine in the treatment of 49 children and adolescents with severe OCD. When desipramine was given to those patients who improved on clomipramine, they experienced a relapse of their obsessive-compulsive symptoms at rates similar to those for placebo in a prior study (Flament et al., 1985).

Children and adolescents with OCD were studied in an 8-week multicenter, double-blind, parallel group trial of clomipramine versus placebo (DeVeugh-Geiss et al., 1992). Efficacy assessments included the NIMH Global Rating Scale and the child version of the Yale Brown Obsessive Compulsive Scale. After 8 weeks, clomipramine-treated patients showed a mean reduction in Yale Brown Obsessive Compulsive Scale scores of 37% versus 8% treated with placebo (DeVeugh-Geiss et al., 1992). Side effects were typical of those seen with TCAs. In a one-year open-label treatment, clomipramine therapy continued to be effective and well tolerated.

In view of their comparable efficacy and more benign side effect profile, we recommend trying at least 2 SSRI (e.g., fluvoxamine, sertraline, paroxetine, fluoxetine) trials prior to initiating clomipramine for most pediatric OCD patients. Exceptions may include contraindication to SSRI and/or a past history of excellent response to clomipramine or strong family history of response to clomipramine with lack of response to SSRIs. Careful monitoring and clear explanation to the parents and children about TCA risks including potential cardiac complications is indicated.

While clomipramine and the other SSRIs have been shown to be superior to placebo in pediatric OCD (see Chapter 9 for more information on SSRIs), as many as one third of all OCD patients do not respond at all to adequate medication trials, and many responders respond only partially (see Grados et al., 1999, for review). Early-onset illness is also associated with increased risk for treatment-refractory OCD (Blanes and McGuire, 1997). This has necessitated investigation of novel treatments.

Simeon and associates (1990), in an attempt to maximize therapeutic effects and minimize adverse effects, treated six adolescents with OCD with clomipramine-fluoxetine combination. The patients were first treated with clomipramine alone. If this was not effective or if side effects developed, fluoxetine was added to the regimen. Clinical global improvement with clomipramine alone was rated as moderate in three patients and minimal in three others. Clinical global improvement with the clomipramine-fluoxetine combination was rated as marked in five patients and moderate in one. These improvements were achieved with relatively low daily doses of clomipramine, 25–50 mg/day, and fluoxetine 20–40 mg/day. The drug combination was well tolerated. Side effects were greater and less tolerable with clomipramine alone than with clomipramine-fluoxetine

combination. The investigators concluded that relatively low doses of the clomipramine-fluoxetine combination may potentiate the therapeutic effects and minimize side effects in patients with OCD. They did not report that any of the patients experienced akathisia. This side effect of fluoxetine treatment may be more common than was previously believed (see Chapter 9). It is possible that clomipramine-fluoxetine combinations may increase this risk. Fluoxetine can dramatically increase TCA levels. Newer SSRIs, particularly fluvoxamine and ataloprain, may represent safer alternatives when used in combination with TCAs such as clomipramine (discussed in detail in Chapter 9). In fact, Figueroa et al. (1998) extended this finding in seven children and adolescents with OCD treated with SSRI-clomipramine combinations other than just fluoxetine who had failed to respond sufficiently to monodrug therapy. In this open-label study, they found that fluvoxamine augmentation of clomipramine did not result in change in clomipramine plasma concentrations or in ECG or other cardiac changes. Nonetheless, they underscored that careful monitoring is essential whenever SSRI-TCA combinations are prescribed. More recently, Fitzgerald and colleagues (1999) reported in an open-label study that risperidone augmentation of clomipramine, paroxetine, or fluoxetine resulted in marked improvement in patients who had either not responded at all to SSRI treatment or who had not responded sufficiently to monodrug therapy. It is emphasized that augmentation with risperidone was effective at very low doses initiated at 0.25 mg/day and increased to a maximum of 1.5 mg/day.

It should be noted that we typically recommend at least two SSRI trials before using clomipramine or considering combination trials. However, some flexibility is required. For example, some patients will experience some improvement that is not sufficient on an SSRI. However, the improvement is noticeable, and children and their families may be reluctant to stop a medication that has been somewhat helpful and then restart another medication that may or may not be effective. The risks/benefits must be considered and explained in detail to the child and his or her parents. Larger controlled trials of combination therapy are clearly warranted. Standard dosage regimens for clomipramine can be found in Table 10.

Case History*

Jane, who is 17 years old, remembers vividly that at age 5 or 6 she repeatedly washed her hands. She said that she needed to “cover each spot” and would wash her hands again and again because of an inner urge to be certain that her hands were clean. This gradually improved over the next few years, but by age 7 or 8 the obsession and compulsion had changed. Jane had enuresis at night until well into the third grade. She would shower, but not feel clean, and would

* From Jensen, 1990.

TABLE 10 Dosage and Regimen of TCAs in Child and Adolescent OCD

Clomipramine:
Drug of choice.
Superior to other antidepressants.
Side effects can be problematic.
Initial dose: 25 mg/day for children <25 kg, 50 mg/day if >25 kg.
Increase dosage weekly by amount equal to subject's initial dose.
Maximum daily dose should not exceed 5 mg/kg or 250 mg.
Addition of fluoxetine can reduce clomipramine dose, enhance efficacy, and decrease side effects.
Combination of fluoxetine 20–40 mg/day or low dose of other SSRI and clomipramine 25–50 mg/day may be best in some patients.
Combination therapy may exacerbate problematic fluoxetine side effects (i.e., akathisia).
Careful monitoring required.
Other TCAs not recommended

have to take two or three more baths per day. The subjective feeling of a lack of cleanliness and of being contaminated did not wash away. As a result, she also had to change her clothes two or three times a day.

When she was 9 years old, Jane experienced a specific precipitating event. While approaching the end of a book, she would feel uncertain about whether she understood it. As she finished the last paragraph, she would have a terrible feeling that she had not read the book correctly and would begin to slowly reread it. She would read and reread each paragraph carefully, going over and over sentences, paragraphs, chapters, and the entire book. Her schoolwork was especially impaired if she had to read out loud. Her pervasive thoughts were that she was not doing her work correctly.

In the summer following the ninth grade, Jane attempted to make herself read and socialize more. She, however, became increasingly more anxious and uncertain. She decided to lose weight so that she would become more acceptable to others. She became markedly depressed. She noticed that her heart would beat fast, that she was short of breath, and that she felt desperate and suicidal. During the early fall of the 10th grade, she found herself overwhelmed with anxiety, unable to concentrate at all on her work, and completely unable to function at school. She was hospitalized in a psychiatric hospital for 6 months. The first 3 months of that hospitalization were in a “short-term” acute-care ward. She was told that her diagnosis was “free-floating anxiety.” She said that talking in group and individual therapy did little to help. She was placed on haloperidol, 5 mg twice daily, with no improvement. Nortriptyline and imipramine were both given

brief clinical trials. She reported that while the drugs helped with the anxiety, they did not ameliorate her major depression, suicidal thoughts, thoughts of guilt, and listlessness. The medication did not help the almost constant thoughts with which she struggled. Finally, she was referred to a behavioral medicine clinic during the last 3 months of the hospital stay, where a therapist gave her cognitive behavioral therapy. She was told to focus on her feelings, instead of her thoughts, and this appeared to help in distracting her from the obsessions. By January of the 10th-grade year, at age 16, she was back in school and seeing her therapist weekly for individual cognitive therapy.

The therapy continued for a year and a half, with more family-oriented focused therapy. The family history included a ruminative, obsessive father. The father, who had impulsive temper outbursts, would often physically assault the mother, twisting her arm, kneeling her in the chest, throwing crystal in the house, and forcing himself on his wife sexually. Jane had been very frightened of him and had been “kidnapped” by him when she was 6 years old. However, he was also a very hard-working studious person, who was at times quite likable.

At the time that Jane was seen for an evaluation for clomipramine, her main obsession continued to be with reading. She would often stop, repeat the reading, and not be able to go on. There was an almost constant preoccupation with checking her schoolwork that required her to spend two or three times longer than necessary doing her homework or schoolwork. She became afraid that she would hurt the children for whom she was baby-sitting, although she had spent the previous summer baby-sitting from 12–13 hours per day. She would ruminate about suicide and what she was doing to prevent self-destruction. As she remembered her wrongdoings, she became more certain that she might harm herself; while having these distressing thoughts, she found that her heart was beating fast and that she could not breathe. She attempted to control these thoughts, although she had very little control. Compulsions were limited to reading and rereading. She said that she became very distressed if anyone interrupted her.

Jane responded poorly to a clinical trial of clomipramine. She continued to have marked difficulty with obsessions and compulsions. Plans for treatment included a trial of exposure in vivo and response prevention, as well as a medication trial with fluoxetine. Jane and her mother were very depressed that the clomipramine had not been successful. Day hospitalization was arranged. Her symptoms were so distressing that she continued to have occasional suicidal ideations of a moderate to a severe degree.

Bulimia Nervosa

The use of antidepressants in the treatment of bulimia nervosa remains controversial. The routine use of TCAs is not recommended, but Mitchell and Groat (1984) recommend them for patients with significant depression. In view of the fact that

TCAs have not been shown to be superior to placebo in the treatment of childhood and adolescent MDD, we do not recommend their use in pediatric bulimic patients with or without depression. SSRIs such as fluoxetine are now FDA-approved for treating bulimia in adults and may also be effective in adolescents with bulimia (see Chapter 9). The risk-benefit ratio is much more favorable for SSRIs such as fluoxetine as opposed to the TCAs.

Anorexia Nervosa

The TCAs have not been found to be effective in treating anorexia nervosa and are not recommended for use in children and adolescents with anorexia nervosa.

Drug Craving/Substance Abuse Disorders

See Chapter 19.

Pervasive Developmental Disorders (Autism)

Clomipramine has been shown to be superior to both placebo and desipramine in treating autistic patients (Gordon et al., 1993). It is important to note that most caregivers elected to continue treatment with clomipramine, underscoring the improvement noted. Further study of clomipramine as well as the other SSRIs is clearly warranted for this severe and typically chronically disabling condition.

McDougle and colleagues (1992) treated five autistic outpatients aged 13, 24, 27, 20, and 33 years with clomipramine. Four of the patients (including the 13-year-old) showed significant improvement in disturbances of social relatedness, OCD symptoms, and/or aggressive and impulsive behavior when treated with open-label clomipramine. The fifth patient remained unchanged. Among the four patients who responded, three improved after 6–8 weeks and one required up to 12 weeks of treatment with clomipramine before significant changes occurred. Mean doses of clomipramine were 185 ± 74 mg/day. Clomipramine blood levels were not obtained during treatment, but each patient lived with responsible parents or group home staff members who administered the medication as prescribed. The authors were not able to determine from this study whether or not the reduction in social withdrawal and aggressivity was a direct effect of clomipramine or an indirect result of the decrease in OCD symptoms (McDougle et al., 1992).

Garber and associates (1992) conducted an open clinical trial of clomipramine for chronic stereotypic and self-injurious behaviors in 11 consecutive patients ranging in age from 10 to 20 years and who had concomitant developmental disorders. Ten patients (91%) showed marked decreases in rates of target behaviors. It is important to note that no seizures occurred despite the fact that six of the patients had histories of epileptic events. Improvement was evident regardless

of the level of mental retardation. Placebo-controlled study is necessary to determine the true role of clomipramine and other SSRIs in treating pervasive developmental disorders.

Night Terrors and Somnambulism

Pesikoff and Davis (1971) reported that four children with night terrors, two children with somnambulism, and one child with both disorders experienced complete remission of their sleep disorders when treated with imipramine (10–50 mg at bedtime). The routine use of imipramine or other TCAs is not recommended because these disorders are often self-limited in children. Pharmacological intervention should be reserved for patients who prove refractory to behavioral interventions and whose sleep disorders result in a threat to physical safety, such as sleepwalking out of the house or falling down stairs. Alternative and safer medications (e.g., benzodiazapines) should also be considered prior to initiating a TCA for these conditions.

Borderline Personality Disorder

The TCAs (and other psychotropic agents including neuroleptics, SSRIs, and MAOIs) have been proposed as a possibly effective pharmacological intervention in borderline personality disorders. Although the data to support this claim are limited, there are some minimal data to suggest the efficacy of TCAs in adults for this condition. The clinician is reminded that an overdose of a TCA can result in death, even if the adolescent arrives at the hospital promptly (Ryan, 1990). Moreover, the dangers of TCA toxicity are greater in children and adolescents than in adults. Borderline personality disorder patients, who are characteristically impulsive and not infrequently make attention-seeking suicide gestures, therefore should not routinely be placed on an agent whose ability to relieve their symptoms is questionable and whose potential to cause harm is great.

Conduct Disorder

Antidepressant therapy has been proposed for conduct-disordered children and adolescents, especially those with an affective conduct disorder. There are limited data demonstrating the effectiveness of antidepressants in this population. Conduct-disordered patients, like patients with borderline personality disorder, are notoriously impulsive and make suicide attempts approximately as often as do depressed patients (but not as many actually kill themselves). Therefore, TCAs are not recommended for use in treating children and adolescents with conduct disorders. They may be useful in treating ADHD with comorbid conduct disorder, particularly if the conduct disturbance is secondary to ADHD. However, psycho-

stimulants are the first-line therapy for this condition. Bupropion may also be considered prior to TCA therapy.

Dysthymia

Although TCAs have been reported to be helpful in treating some cases of dysthymia in adults, they are more effective in the treatment of depression. Antidepressants can improve a major depressive episode but sometimes not affect the dysthymia (“double depression”). Given the lack of evidence of the efficacy of the TCAs in dysthymic children and adolescents and children and adolescents with major depression, we do not recommend their use in this population.

Attention-Deficit Disorder Without Hyperactivity

Attention-deficit disorder (ADD) without hyperactivity often requires psychopharmacological intervention. Wender (1988) has reported that when used to treat ADHD, TCAs improve mood and decrease hyperactivity, but usually are sedating and do not improve concentration. Therefore, firm guidelines regarding the administration of TCAs to ADD patients without hyperactivity cannot be established. Prescribing a nonheterocyclic antidepressant such as bupropion may merit consideration as it appears not to adversely affect cognition and to be less sedating (see discussion of bupropion, Chapter 10).

Trichotillomania

Swedo and colleagues (1989) performed a double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania and found mean daily doses of 180 mg/day of clomipramine to be effective. Significantly, desipramine was not found to be effective in the treatment of trichotillomania. Further study of clomipramine and other SSRIs in pediatric patients with this condition is clearly warranted.

Posttraumatic Stress Disorder

There are no truly effective psychopharmacological treatments for the core symptoms of posttraumatic stress disorder (PTSD). Because of the lack of conclusive evidence of the efficacy of TCAs in the treatment of child and adolescent depression, anxiety, and panic symptoms, we do not recommend their use in pediatric PTSD patients.

Chronic Pain Syndromes

The overlap of physical and psychiatric symptoms in chronic pain syndromes often creates diagnostic and therapeutic difficulty. In adults, TCAs have been

shown to be beneficial in the treatment of chronic pain syndromes. Imipramine has been shown in animal studies to potentiate morphine analgesia. In adults, imipramine and amitriptyline have been effective in reducing chronic pain associated with diabetic neuropathy (Kuinesdal et al., 1984). Analgesic effects of amitriptyline are seen with antidepressant levels lower than those usually effective in the treatment of adult MDD. Low-dose therapy (i.e., 100–150 mg of imipramine/day) is recommended for the initial treatment of chronic pain in adults, although doses can be increased to the 150–300 mg/day range (Arana and Hyman, 1991). There are no data on children and adolescents. It is not uncommon, however, for TCAs to be used in chronic pain syndromes (e.g., migraine), particularly with associated sleep disturbance. We recommend trying alternative approaches given the lack of data in children and the potentially hazardous side-effect profile of the TCAs.

CONTRAINDICATIONS

See Table 11.

Pregnancy

In general, TCAs should not be administered during pregnancy, although there may be exceptional cases, such as a woman who has been shown to clearly respond to a particular TCA and who is known to decompensate (i.e., become suicidal) when the medication is withdrawn. This is a decision that requires a great deal of consideration and collaboration with the obstetrician, and it is imperative that the risks versus benefits be fully discussed. In adults, we recommend trying to taper the TCA whenever possible, but if the family and/or patient is unwilling and/or the clinician believes this to be a direct threat to the patient's

TABLE 11 Contraindications to TCA Therapy

Absolute:

- Pregnancy
- Prior hypersensitivity reaction
- Currently on MAOI

Relative:

- Epilepsy
 - Psychosis (i.e., schizophrenia)
 - Cardiac
 - Thyroid
 - Diabetes?
-

life, medication can be continued with close monitoring, such as with ultrasound or physical examination.

Since TCAs are secreted in breast milk, mothers should be discouraged from breast-feeding if they are taking TCAs.

Allergy

A history of hypersensitivity to TCAs is a contraindication to TCA therapy.

Cardiac Conduction Anomalies

Cardiac disorders must be approached cautiously when TCA therapy is being considered (see Side Effects).

MAOI Therapy

A TCA should not be administered while a patient is receiving an MAOI and should not be initiated until the patient has been off the MAOI for at least 2 weeks. It should be noted that an MAOI can be added to an ongoing TCA regimen that has only been partially effective (Ryan et al., 1987c) (see Chapter 11). Adding an MAOI to a TCA is relatively safe for desipramine and nortriptyline provided there is careful monitoring, but this is contraindicated when imipramine or amitriptyline is being administered. Pare and colleagues (1982) argue that a TCA-MAOI combination may provide relative protection against tyramine-induced hypertension. We do not recommend this combination in children and adolescents.

Epileptic Patients

Patients with epilepsy are vulnerable because TCAs can lower the seizure threshold. Epileptic patients are more vulnerable to mood disorders (see Chapter 18). When a patient is on a stable anticonvulsant regimen, this is not generally problematic. Careful monitoring of anticonvulsant and antidepressant levels is necessary, and dose adjustment may be necessary.

Thyroid Dysfunction

The use of TCAs in patients with thyroid dysfunction must be approached cautiously, because this condition can induce cardiac arrhythmias (Kaplan and Saddock, 1991).

Diabetes

Theoretically, TCAs could increase glucose levels (Ryan, 1990). However, many adult diabetics who are depressed are treated with TCAs. Careful monitoring of glucose levels is recommended.

SIDE EFFECTS

See Table 12.

Cardiac

Mild increases in the PR interval (5–10%), QRS duration (7–25%), and prolongation of the QT interval (3–10%) are common in children and adolescents (Ryan, 1990; Gutgesell et al., 1999). A corrected QT interval (QTc) of >460 msec has been reported in 8% of patients treated with TCAs, but mean QTc intervals remained within the normal range in pediatric patients treated with TCAs (Biederman et al., 1989a; Schroeder et al., 1989; Fletcher et al., 1993; Wilens et al., 1993, 1996). A mild increase in the pulse rate of up to 120 beats per minute with sinus tachycardia is not uncommon and is frequently asymptomatic (Ryan, 1990; Gutgesell et al., 1999). Large increases in cardiac conduction slowing (i.e., PR > 0.21 and QRS > 0.12) can be dangerous and can result in arrhythmias and/or heart block. Torsade de pointes and other malignant arrhythmias have not been reported in children and adolescents treated with TCAs except for ventricular fibrillation resulting in sudden cardiac death in a patient who had a family history of sudden death (Gutgesell et al., 1999).

Cardiovascular side effects are of particular concern in children and younger adolescents because of the efficiency with which they convert TCAs to potentially toxic 2-hydroxy metabolites (Ryan et al., 1987a; Baldessarini, 1990). These patients appear to be more sensitive to cardiac toxicity than are older ado-

TABLE 12 Side Effects of TCAs
in Children and Adolescents

Cardiac
Anticholinergic
Psychosis
Mania
Seizures
Hypertension
Confusion
Insomnia/nightmares
Rash
Tics
Tremor
Incoordination
Anxiety
Sexual dysfunction
Photosensitization

lescents and adults (Baldessarini, 1990). In fact, there is greater variability in heart rate in children than in adults (Geller et al., 1999). Interestingly, desipramine treatment has been found to significantly decrease variability of heart rate (Walsh et al., 1994; Mezzacappa et al., 1998). Age-associated effects of desipramine on variability of heart rate were not observed.

In an attempt to minimize cardiac side effects associated with peak TCA plasma levels in children, Dugas and associates (1980) recommended giving divided doses—b.i.d.-t.i.d. dosages for total daily doses of over 1 mg/kg. Administering the total daily dose at one time, e.g., bedtime, is not recommended for children. Ryan and associates (1987a) did, however, observe that, once the dosage was stabilized, the total daily dose of imipramine could be safely given to adolescents at bedtime without increasing the risk of cardiac side effects.

Increased risk for cardiovascular side effects may also be associated with concomitant use of other medications, including methylphenidate, which decreases TCA metabolism, and cimetidine, which increases TCA plasma levels (Gutgesell et al., 1999) (see also Drug Interactions). The actions of sympathomimetic agents (commonly found in cold preparations) can also be increased with TCA administration.

Familial History

Sudden cardiac death and syncope have been associated with family history of prolonged QT intervals and torsade de pointes (Gutgesell et al., 1999). Therefore, drugs that can prolong the QT interval, including TCAs, may be contraindicated in children and adolescents with familial prolongation of the QT interval and torsade de pointes. It should be noted that it may be difficult to elicit a family history of prolongation of the QT interval and torsade de pointes from patients and their families. Many families may not know these specifics, although they may be aware of a family member who died of a heart attack, sudden death, etc. Obviously, it also may not be possible to screen for familial prolongation of the QT interval and torsade de pointes in adopted children and adolescents where familial records may not be available. In all cases, careful monitoring (discussed below) is warranted when TCAs are administered to children and adolescents.

Sudden Death

Of greatest concern are the reports of sudden cardiac deaths of children on TCAs. At least 7 deaths in pediatric patients have been associated with the TCAs imipramine and desipramine (Abramowicz, 1990; Biederman, 1991; Riddle et al., 1991, 1993; Popper and Zimnitzky, 1995; Varley et al., 1997). Although the actual relationship between TCAs and sudden death is not known, Leonard et al. (1995) reported EKG changes associated with long-term maintenance TCA (desipramine and clomipramine) treatment in children and adolescents who were not observed

after short-term TCA treatment. This underscores the importance of close monitoring (described below).

Some cases of sudden death have been associated with toxic plasma TCA levels (Gutgesell et al., 1999). One patient had a known risk factor for sudden death (documented coronary abnormality), and there was a family history of sudden death in another case of sudden death associated with TCA treatment. Saraf and colleagues (1974) reported the case of a 6-year-old girl receiving imipramine for separation anxiety and school phobia who died 3 days after the dose had been raised to 300 mg at bedtime, or almost 15 mg/kg. Treatment guidelines for the use of TCAs recommend not exceeding daily doses of 5 mg/kg (Sudden death, 1990). This death is believed to have been directly due to treatment with an excessive dose of imipramine and inadequate monitoring. Surprisingly little is known about most of the cases of sudden cardiac death associated with desipramine (Biederman, 1991). These deaths have been presumed by many to be due to cardiac abnormalities. It is not known, however, whether the patients had pre-existing medical and/or cardiac abnormalities, how they were monitored, and whether dosages had recently been increased (as was the case for the girl treated with imipramine) (Biederman, 1991).

One death was that of an 8-year-old boy who had been treated for ADHD with unknown desipramine doses for 2 years and who had no known cardiac disease. Another 8-year-old boy with ADHD died of sudden cardiac arrest after being treated with desipramine 50 mg/day for 6 months. Yet another case involved a 9-year-old boy who was treated with desipramine for an unknown time and with unknown dosages. Levels of desipramine drawn after cardiac arrest were reportedly “therapeutic or subtherapeutic” in all three of the aforementioned cases.

These sudden deaths have generated concern regarding the safety of TCAs in young children, especially at daily doses greater than 3.5 mg/kg. Winsberg and colleagues (1975) found that three of seven children (43%) receiving imipramine at daily doses of 5 mg/kg developed asymptomatic prolongation of the PR interval of up to 180 msec without a significant relationship to steady-state blood levels of the medication. Preskorn and associates (1983) noted that with imipramine at daily doses of up to 5 mg/kg, decreased conduction efficiency (as measured by an ECG) was found when imipramine plus desipramine levels were greater than 250 ng/mL. Biederman and colleagues (1985, 1989a, 1989b, 1995) have studied the cardiovascular effects of desipramine in over 200 children and adolescents, evaluating the associations among dose, plasma levels, and cardiac complications. They have consistently found small, clinically asymptomatic, but statistically significant increases in heart rate, diastolic blood pressure, and ECG conduction parameters associated with desipramine therapy at daily doses of up to 5 mg/kg. Documented ECG evidence of atrioventricular (AV) block (i.e., PR \geq 200 msec) was observed in only 0.5% of cases. Complete AV conduction

defect of the right bundle branch type (i.e., QRS \geq 120 msec) was observed in 3% of the cases. Eighteen percent of the patients at drug-free baseline examination and 35% of the cases with new manifestations on desipramine showed evidence of sinus tachycardia (heart rate \geq 100 beats/min), and 10% of baseline patients and 23% of new cases on desipramine showed evidence of incomplete right bundle branch block (i.e., QRS 100–120 msec). It is important to note that Biederman and colleague's data (Hayes et al., 1975; Silber and Katz, 1975; Glassman et al., 1981; Biederman et al., 1989a) do not confirm the hypothesis that prepubertal children may be at increased risk for cardiac side effects (Biederman et al., 1985, 1989a, 1989b). Biederman and colleagues (1989a, 1991) emphasize that since 10% of healthy children meet ECG criteria for incomplete right bundle branch block and 18% for sinus tachycardia, it is vital to obtain ECGs in these patients at baseline while medication-free.

The clinical significance of the aforementioned cardiovascular findings remains unclear. TCA-induced sinus tachycardia and delays in intracardiac conduction rarely appear to be clinically significant in noncardiac adult and child patients (Puig-Antich et al., 1979, 1987; Glassman and Bigger, 1981; Veith et al., 1982; Preskorn et al., 1983; Glassman et al., 1983; Biederman et al., 1985; Roose et al., 1987). Prolongation of the PR interval in the absence of AV conduction block is generally not clinically significant and does not result in hemodynamic compromise (Biederman et al., 1991, 1989a). In fact, incomplete right bundle branch block is a normal ECG finding in children up to 10 years of age. Nonetheless, the development of incomplete right bundle branch block in children being treated with TCAs necessitates close clinical and ECG monitoring, especially at doses greater than 3.5 mg/kg/day (Biederman et al., 1989a, 1991). Complete right bundle branch block in a child with a healthy heart does not necessarily imply impaired cardiac function. Its development does, however, necessitate assessment of cardiac ejection fraction and cardiac output, since it decreases the electromechanical function of the right ventricle (Biederman et al., 1989a, 1991). It is important to note that right bundle branch block in the presence of preexisting cardiac disease has more serious complications. It is, therefore, recommended that in patients who have congenital heart disease, murmurs, acquired heart impairment, rhythm disturbances, a family history of serious cardiac disease (sudden cardiac death), or diastolic hypertension (>90 mmHg), or when the cardiac status of the child is uncertain, additional cardiac evaluation be undertaken (Biederman et al., 1989a, 1991). The evaluation should include a 24-hour Holter monitor and echocardiogram (Biederman et al., 1989a). This can help in assessing the potential benefits versus the risks of treating patients with TCAs.

It must also be emphasized that sinus tachycardia, which is not uncommon in children treated with TCAs, was found in 20% of Biederman and colleagues' (1985, 1989a, 1989b) patients at drug-free baseline evaluation. In older children and adolescents, however, a heart rate that remains persistently above 130 beats

per minute is of concern and should prompt further noninvasive cardiac evaluation, including Doppler echocardiography, to assess ventricular ejection fraction and cardiac output (Biederman et al., 1989a).

It is known that toxic concentrations of TCAs (i.e., after an overdose) can significantly depress myocardial conduction (see Overdose). Therapeutic doses of these agents, however, appear to be safe and have little adverse effect on left ventricular ejection fraction in adults, even in those with diagnosed cardiac disease (Veith et al., 1982; Roose et al., 1987). It also appears that cardiovascular changes associated with imipramine and desipramine are rapidly reversible when the TCA dose is decreased or discontinued (Puig-Antich et al., 1979, 1987a). But it should be noted that this issue has not been evaluated adequately in children treated with TCAs and that the reversibility of such cardiac complications in children has not been systematically assessed (Biederman et al., 1989a, 1991).

Treatment with TCAs at doses above 3.5 mg/kg or at plasma levels greater than 150 ng/mL may increase the risk of asymptomatic ECG changes, particularly a slight prolongation of the PR interval and moderate increases in the QRS duration (Biederman et al., 1989a, 1991). Delayed cardiac conduction and minor increases in diastolic blood pressure and heart rate can also be seen.

It is not known whether or not children treated with TCAs have a higher risk for sudden death than do untreated children or children receiving different treatments. It should be noted that this is not the first time that concern has been raised regarding a possible association between the use of TCAs and sudden cardiac death. Coull and colleagues (1970) reported that 6 of 53 patients with cardiac disease died suddenly after receiving amitriptyline, while there were no sudden cardiac deaths in control patients. The Boston Collaborative Drug Surveillance Program (1972) monitored adverse reactions to TCA drugs and failed to confirm this finding.

At the present time, no causal link between sudden cardiac death and TCA use has been established. It is important to remember that adverse, idiosyncratic reactions can be seen with any medication (Biederman et al., 1989a, 1991). Genetic anomalies are also seen in the population and may be contributory in some cases. It is not known how many children have been treated with TCAs, although the number is believed to be quite large. This suggests that if such a risk exists, it most likely is small (Biederman et al., 1989a, 1991). Utilizing an epidemiological approach, Biederman and colleagues have generated some new data on the ‘‘sudden death’’ phenomenon in children and adolescents on TCAs. Their results suggest that sudden death from TCAs is an extraordinarily rare event when therapeutic plasma levels are used (personal communication). Nonetheless, this potential risk and other side effects need to be taken into account when TCA therapy is considered. For example, in depressed children with known cardiovascular impairment, the TCAs would not be recommended. On the other hand, a child with ADHD who has not responded to any other pharmacological or behavioral

interventions and whose disruptive behavior causes severe problems for the patient, family, and school and peers may warrant a TCA trial since these agents have been shown to be superior to placebo in treating ADHD.

Although clinicians should not be so alarmed that they absolutely refuse to prescribe TCAs in all or any situations, careful monitoring is essential in these patients. Equally critical is adequate explanation of the risks/benefits to the patient and family.

Table 13 presents cardiac, ECG, and blood pressure guidelines for the use of TCAs in children and adolescents. The American Heart Association (Gutgesell et al., 1999) specifically recommends a comprehensive baseline history and physical examination, detailed delineation of current medication history, family history assessment for cardiac disease, baseline ECG measuring (PR \leq 200 msec, QRS duration \leq 120 msec, QTc \leq 460 msec), and follow-up ECG and history after achieving a steady-state level of the TCA on 3–5 mg/kg for desipramine or imipramine.

Anticholinergic

Dry mouth and constipation are frequently seen in both children/adolescents and adults. Fortunately, these side effects are usually dose dependent and often dissipate with time. Blurred vision and urinary retention are believed to be less common in children and adolescents than in adults (Ryan, 1990).

Psychosis/Mania

Psychosis is an uncommon but potentially serious adverse side effect of TCA therapy (Ryan, 1990). Antidepressant-induced mania is a well-described, albeit uncommon, side effect (Bunney et al., 1972; Wehr and Goodwin, 1981; Lensgraf and Favazza, 1990).

Seizures

All of the antidepressants can decrease the seizure threshold, although this side effect is uncommon. The risk of seizures is highest in children and adolescents with neurological disorders and/or abnormal neurological examination (Ryan, 1990). Maprotilene is the TCA most associated with increasing the risk of seizures, especially at doses greater than 300 mg/day. This has led many investigators to call for its withdrawal. Great caution should be employed in its use.

Hypertension

Hypertension is an uncommon side effect. It is usually clinically significant only when there is preexisting hypertension (Ryan, 1990).

TABLE 13 ECG and Blood Pressure Guidelines for the Use of TCAs in Children and Adolescents^a**A. ECG**

Baseline ECG must be done in all patients before starting treatment with TCAs (for ECG, BP, and pulse parameter, see below).

For doses greater than 25 mg/day, ECG rhythm strip should be obtained before each TCA dose increase or when TCA reaches the steady state (3–5 days).

During maintenance, ECGs or rhythm strips will be repeated at least once every 3 months.

Tricyclic antidepressants will be reduced or discontinued if:

PR interval: patient ≤ 10 years of age and PR interval is >0.18 ; patient is >10 years old and PR interval is >0.20 .

QRS Interval: >0.12 second or widening more than 50% over baseline QRS interval.

Corrected QT: ≥ 0.48 second.

Heart rate: Patient is ≤ 10 years of age and resting heart rate is >110 ; patient is >10 years of age and resting heart rate is >100 .

B. Blood pressure (BP)^b

The child should be in a comfortable, sitting position and sufficient time should be allowed for recovery from recent activity or apprehension.

For inpatients, BP and pulse should be measured at least three times a week.

For outpatients, during dose titration, BP and pulse should be done at least once a week. During maintenance, BP and pulse should be taken at least once a month (if it is possible, we recommend that the school nurse take more frequent BP and pulse readings and call us if the patient has questionable readings or they meet the criteria for lowering or discontinuing TCAs).

The manometer must be well calibrated and proper cuff size should be used (long enough to completely encircle the circumference of the arm—with or without overlap—and wide enough to cover approximately 75% of the upper arm between the top of the shoulder and olecranon).

Tricyclic antidepressants will be reduced or discontinued if: patient is ≤ 10 years of age and resting BP $\geq 140/90$ or if BP is persistently greater than 130/85 (50% of the time during 3 weeks).

C. Patients who must continue treatment with TCAs and have questionable or borderline BP and/or ECG or they meet the above criteria for lowering or discontinuing TCAs will be referred to the pediatric cardiology department at Children's Hospital for further evaluation and Holter monitoring.**D. Lying and standing BP and pulse may be obtained to assess possible orthostatic hypotension at the discretion of the physician.**

^a These criteria were developed by Dr. James Zuberbuhler and Dr. Lee Beerman (Children's Hospital of Pittsburgh). These guidelines are empirical and subject to change.

^b *Note:* These BP guidelines were made under the assumption that patients will remain on treatment with TCAs for 6–9 months.

Confusion

Confusion most often is secondary to anticholinergic toxicity and has been reported with higher TCA plasma levels (Preskorn et al., 1983). Preskorn and colleagues (1988) did observe cognitive toxicity in children that was associated with subtherapeutic plasma TCA levels.

Insomnia/Nightmares

Nightmares and insomnia are relatively uncommon side effects of TCAs in children and adolescents (Ryan, 1990).

Rash

An allergic reaction to TCA therapy is relatively rare. Such a reaction may be caused by tartrazine, the FD&C Yellow No. 5 dye used in some TCA formulations (Ryan, 1990). It should be noted, however, that some allergic reactions do appear to result from the active ingredients as well.

Tics/Incoordination/Tremor/Anxiety/Photosensitization

Tics, incoordination, tremor, anxiety, and photosensitization are occasional side effects of TCAs (Ryan, 1990).

Sexual Dysfunction

Breast enlargement and galactorrhea have been reported occasionally in females treated with TCAs (Ryan, 1990). Gynecomastia in males has also been reported. Increased libido, decreased libido, and impotence have been observed as well.

OVERDOSE

The TCAs have a very high potential for causing death when taken in overdose (Ryan, 1990), even if the child is taken to the hospital immediately after the event. When a patient overdoses on more than 1 g of a TCA, toxicity often results and death can occur (Arana and Hyman, 1991). Heart arrhythmias, seizures, hypotension, etc. can result in death (Arana and Hyman, 1991). It should be noted that, as in adults, plasma TCA levels often do not reflect the severity of the overdose (Ryan, 1990). Fatal arrhythmias can occur in patients with therapeutic and relatively modest TCA blood levels. Almost all symptoms develop within 24 hours of the overdose (Arana and Hyman, 1991).

Central nervous system side effects ranging from drowsiness to coma are common (Arana and Hyman, 1991). These side effects can be exacerbated and potentiated if the patient has also ingested other CNS depressants, such as benzo-

diazepines, alcohol, or barbiturates (Arana and Hyman, 1991). Antimuscarinic side effects are frequent and often pronounced and include dry mucous membranes, warm dry skin, blurred vision, and mydriasis (Arana and Hyman, 1991); cardiovascular toxicity may also occur. Respiratory arrest and uncontrolled seizures can result from a severe overdose (Arana and Hyman, 1991).

Treatment of Overdose

In the event of an overdose, it is essential to provide close cardiac and respiratory monitoring. When decreased ventilation is noted, ventilatory assistance is indicated. Hypotension may necessitate the administration of fluids. Pressors such as epinephrine may be necessary if hypotension is severe or does not abate with simple fluid replacement. Epinephrine is the medication of choice in this situation because it can counteract the anti- α -adrenergic side effects of the TCA (Arana and Hyman, 1991). Continuous cardiac monitoring in the intensive-care setting is required for any patient with arrhythmia and/or QRS duration greater than 0.12 ms. Serum TCA levels should be closely monitored, and cardiac monitoring should be continued until the arrhythmias and the QRS have normalized and plasma TCA levels are no longer toxic. We wish to reemphasize that TCA levels do not always reflect the severity of TCA overdose, and fatal arrhythmias can occur in patients with modest plasma TCA levels (Ryan, 1990).

Sinus tachycardia often does not necessitate treatment (Arana and Hyman, 1991). Direct-current cardioversion may be indicated for supraventricular tachycardia causing hypotension or myocardial ischemia (Arana and Hyman, 1991). Propranolol is safe and effective in the treatment of recurrent supraventricular tachycardia, but digoxin is contraindicated because it can precipitate or exacerbate heart block (Arana and Hyman, 1991). In those patients with ventricular tachycardia or ventricular fibrillation, cardioversion is the treatment of choice. Administration of a loading dose of lidocaine and a drip of 2 mg/min may decrease the risk of recurrence (Arana and Hyman, 1991). It should be noted that doses of lidocaine higher than 2 mg/min may increase the risk for seizures. If lidocaine is unsuccessful in alleviating arrhythmias, propranolol and bretylium are then indicated. Quinidine, disopyramide, and procainide are contraindicated for patients who have overdosed on TCAs because they may prolong the QRS and precipitate heart block. Physostigmine also is not effective in treating TCA-induced arrhythmias (Arana and Hyman, 1991). Temporary pacemakers may be necessary in cases of second- and third-degree heart block.

If the patient is alert, emesis induction is indicated (Arana and Hyman, 1991). Intubation and gastric lavage are necessary if the patient is not alert. In addition, 30 g of activated charcoal with 120 cc of magnesium citrate should be given to reduce the absorption of residual drug, since bowel motility may have been slowed (Arana and Hyman, 1991).

Seizures can be problematic in patients who have overdosed on TCAs, particularly maprotilene. Benzodiazepines such as diazepam or lorazepam are the first-line treatment for TCA-induced seizures. Diazepam should be administered in doses of 5–10 mg IV at a rate of 2 mg/min (Arana and Hyman, 1991). This may be repeated every 5–10 minutes until the seizures are controlled. The risk of respiratory decompensation secondary to benzodiazepine use can be minimized by administering IV benzodiazepines slowly. Lorazepam should be administered in doses of 1–2 mg IV over several minutes (Arana and Hyman, 1991). Lorazepam's advantages over diazepam include its longer effect when administered acutely (hours vs. minutes), a possible lower risk of respiratory depression, and IM availability. Intravenous administration can be problematic in youngsters, and the problem can be exacerbated if the patient is thrashing about. If benzodiazepines are unsuccessful in treating seizures, phenytoin is indicated. A loading dose of 15 mg/kg not exceeding 50 mg/min is recommended (Arana and Hyman, 1991). When phenytoin is given too rapidly (>50 mg/min), severe hypotension may result.

We also wish to emphasize that forced diuresis and dialysis are not helpful because of the tissue binding of TCAs. Indeed, these interventions may increase hemodynamic compromise (Arana and Hyman, 1991).

ABUSE

The TCAs have a low risk for abuse. Anticholinergic side effects are very rarely used to induce an altered mind state (Ryan, 1990).

DRUG INTERACTIONS

See Table 14.

AVAILABLE PREPARATIONS AND COSTS

See Table 15 and FDA guidelines Table 16.

INITIATING AND MAINTAINING TREATMENT

Before Starting Medication

We wish to underscore that the TCAs are not considered first-line pharmacological intervention for any pediatric neuropsychiatric disorder (Geller et al., 1999). Careful weighing of the risks, particularly potential cardiac side effects, versus potential benefits must always be considered. We recommend documenting informed consent from the parents and assent from the child (when possible) and

TABLE 14 Drug Interactions of TCAs

May increase effect of:
CNS stimulants
CNS depressants
MAOIs
Sympathomimetics (i.e., ephedrine)
Alcohol
Antipsychotics
Benzodiazepines
Barbiturates
Anticholinergic agents
Thyroid medications (cardiac effects)
Seizure-potentiating drugs
Phenytoin
May decrease effects of:
Clonidine
Guanethidine
Effects may be increased by:
Phenothiazines
Methylphenidate
Oral contraceptives (estrogen)
Marijuana (tachycardia)
Effects may be decreased by:
Lithium
Barbiturates
Chloral hydrate
Smoking

explaining in detail the risks, particularly the potential cardiac side effects of these medications prior to initiating a TCA trial.

Prior to initiating a TCA trial, children and adolescents should have a physical examination, with special attention paid to heart rate, blood pressure, weight, and height.

To detect a preexisting cardiac conduction defect, a baseline ECG is required (Ryan, 1990). Thereafter, an ECG rhythm strip should be obtained in children younger than 16 years of age at each dose increase and at frequent intervals during the period of dose elevation (Ryan, 1990). We recommend that older adolescents receive close monitoring as well. In fact, we advocate using the same guidelines as recommended for initiating and maintaining TCA therapy in children younger than 16 years of age. Because they are relatively noninvasive tests that are not particularly unpleasant or painful, the benefits of obtaining ECGs outweigh any minor inconveniences, especially in view of the potentially devasta-

TABLE 15 Available Preparations and Cost of TCAs

Drug	Commercially available preparation	Dosage forms	Average cost/day
Imipramine	Generic	10, 25, 50 mg tablets 75, 100, 125, 150 mg capsules	\$0.23
	Tofranil Imipramine pamoate (Tofranil-PM)	10, 25, 50 mg unscored tablets 25 mg/2 mL IM injection (rarely, if ever, used in child and adolescent psychiatry)	
Desipramine	Norpramin	10, 25, 50, 75, 100, 150 mg tablets	\$2.22
	Pertofrane	25, 50 mg capsules	
Amitriptyline	Generic	10, 25, 50, 75, 100, 150 mg tablets	\$0.16
	Elavil	10, 25, 50, 75, 100, 150 mg unscored tablets	
	Endep	10, 25, 50, 75, 100, 150 mg scored tablet (injectable form rarely, if ever, used in child and adolescent psychiatry)	
Nortriptyline	Pamelor	10, 25, 50, 75 mg capsules Oral solution (equivalent to 10 mg/5 mL)	\$2.11
Maprotiline	Generic	25, 50, 75 mg tablets	\$2.31
	Ludiomil	25, 50, 75 mg scored tablets	

Source: Red Book Annual Pharmacist Reference, 1991–1992. Oradell, NJ: Medical Economics Co.

TABLE 16 FDA Guidelines

Drug name	Age limit	Dose limit	Indications
Imipramine	6 years for enuresis	2.5 mg/kg/day for children	Depression in adults and adolescents; enuresis in children
Desipramine	Not recommended for children	150 mg/day	Depression in adults and adolescents
Amitriptyline	12 years	300 mg/day	Depression in adults and adolescents
Nortriptyline	Not recommended for children	150 mg	Depression in adults and adolescents
Maprotiline	18 years	225 mg	Major depression
Trazodone	18 years	600 mg	Major depression
Fluoxetine	No mention	80 mg	Major depression
Bupropion	No mention	450 mg/day	Major depression

Source: Physicians' Desk Reference, 2001.

ting consequences of failing to pick up a previously undetected cardiac anomaly. With reports of sudden cardiac death, the clinician cannot be faulted for exercising caution when prescribing TCAs. It is also important to elicit any family history of cardiac disease.

The TCAs do cross the placenta, so that a pregnancy test and evaluation for adequate contraceptive use is advised in females of childbearing age, since these medications should not be prescribed during pregnancy. Oral contraceptives containing estrogen can increase the effects of TCAs. Indeed, toxicity can occur via inhibition of TCA metabolism. Patients should also be observed for tics and involuntary movements on starting medication. A complete blood count and differential should generally be obtained at baseline. Liver function should also be checked since TCAs are metabolized by the liver.

It is vital that the clinician prescribing TCAs take a thorough substance abuse history. When these agents are taken in combination with marijuana, sinus tachycardia may become prominent (see Chapter 19). Nicotine may decrease the effects of the TCAs by increasing their metabolism, thereby lowering plasma levels. The TCAs can also increase the CNS effects of alcohol (see Drug Interactions).

When Treatment Is Initiated

When children and adolescents are treated with TCAs, it is important to check blood pressure, pulse, and ECG rhythm strip at each dose increase (see Table 13 for cardiac guidelines). Plasma TCA levels should be drawn 5–7 days after the last dose increase and 12 hours after the most recently administered dose. Children and adolescents should have an annual physical examination by their pediatrician or family practitioner.

Dry mouth is a frequently encountered side effect, and it may be ameliorated by reducing the dose or by using sugar-free gum or candy. Rarely, bethanechol, a cholinergic agonist, can be used in doses of 10–50 mg q.i.d. to reduce this symptom when conservative measures are unsuccessful. The only common side effect of bethanechol therapy is stomach cramps, which necessitates lowering the dose (Ryan, 1990).

Constipation, another commonly encountered anticholinergic side effect of TCA therapy, can often be managed with Colace or Metamucil. Laxatives should not be used. Bethanechol would also help, but we recommend using stool softeners or bulk first.

When the more serious anticholinergic complication of delayed urination occurs (which is rare in children and adolescents), dose reduction and/or bethanechol treatment is warranted.

Confusion is often a sign of anticholinergic toxicity and requires prompt intervention. This requires dosage reduction or administration of physostigmine.

If a seizure occurs, immediate discontinuation of the medication is advised until a seizure workup has been completed (Ryan, 1990). If a neurological workup concludes that the seizure was drug-induced, then an anticonvulsant may be added to the regimen. Anticonvulsant prophylaxis permits the antidepressant to be restarted and eventually returned to full dosage.

Finally, if an allergic reaction occurs during TCA therapy, discontinuation of the medication is advised until a complete medical workup has been completed. Lowering the dose temporarily and consulting a dermatologist or switching to a structurally unrelated antidepressant is recommended.

Interference with Diagnostic Blood Tests

These agents can interfere with a number of diagnostic tests, such as increasing the blood levels of cholesterol, aspartate transaminase (SGOT), alkaline transaminase (SGPT), bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, eosinophils, catecholamines, and glucose. They can also decrease blood glucose levels, granulocytes, and platelets.

Dispensing TCAs

As discussed earlier, TCAs have a potential for causing death, either in accidental or deliberate overdose. Therefore, it is absolutely essential that they be kept under careful supervision. Locking them away in child-protective containers, especially if there are infants or young children in the household, is advised. With regard to adolescents, it is vital that both the parents and physician assess whether the patient is capable of reliably and safely taking his or her own medication. In cases where the adolescent is known to be impulsive, it may be advisable to have the parents dispense the medications until the adolescent has demonstrated that he or she can take them responsibly. We also advocate prescribing no more than a 2-week supply of medication at one time. If the patient visits are scheduled at intervals longer than 2 weeks, writing a prescription for a 2-week supply with one or two refills is recommended.

Treatment Duration

There are no firm guidelines as to how long to continue treatment with TCAs for children and adolescents with psychiatric disorders. Since they are not considered first-line medication for any psychiatric conditions in childhood and adolescence, it is difficult to offer definitive guidelines on the use of these agents. Our recommendations are based on a review of the available literature and on clinical experience.

Withdrawal of Medication

Children are at higher risk than adults for experiencing withdrawal symptoms when TCAs are discontinued because they metabolize these medications more

rapidly than do adults (Ryan, 1990). In fact, children commonly show daily withdrawal effects on regular once-daily dosing, and these agents often need to be given in two or three divided doses daily for prepubertal children and younger adolescents (Ryan, 1990). Withdrawal symptoms of TCAs are similar in children and adults, including anxiety, agitation, disrupted sleep, behavioral activation, and somatic or GI distress (Dilsaver and Greden, 1984). The symptoms often give the overall impression of a flu-like syndrome and are largely related to the anticholinergic effects (Ryan, 1990). On withdrawal of TCAs, the anticholinergic effects are responsible for the resultant withdrawal effects. These can be avoided or minimized by gradually tapering the medication over a period of 2 weeks. If withdrawal symptoms do occur, they can be treated by restarting the medication and/or tapering it more gradually (Ryan, 1990).

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9

Selective Serotonin-Reuptake Inhibitors

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The selective serotonin-reuptake inhibitors (SSRIs) have become drugs of first choice for many psychiatric conditions including major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bulimia, panic and other anxiety disorders, among others. SSRIs appear to be comparable in efficacy to the tricyclic antidepressants (TCAs) in adults but have fewer side effects, are far less lethal in overdose, and are likely to have more clinical indications (Emslie et al., 1999). Moreover, recent investigation has suggested the efficacy of the SSRIs, fluoxetine (Emslie et al., 1997, 2000), and paroxetine (Keller et al., 2001) in child and adolescent MDD, whereas the TCAs have consistently demonstrated no superiority over placebo in pediatric MDD (see Chapter 8). Brophy (1995) reported over 200,000 prescriptions and refills of fluoxetine and sertraline for children 5–10 years of age in 1994, representing a fourfold increase in a 2-year period. Increased use of SSRIs and other psychotropic agents, particularly the psychostimulants, in younger children has resulted in additional investigation into prescribing practices (Zito et al., 2000) and questions as to whether these medications have been overprescribed. While investigation to date raises many more questions than are answered, i.e., who is prescribing the medications, conditions being treated, etc, there is no question that these medications are being prescribed with a minimum

of extant controlled research study (Emslie et al., 1999). While this chapter underscores the growing need for additional research investigation to better delineate the clinical efficacy vs. toxicity of the SSRIs as well as many other psychotropic medications in children, we have attempted to synthesize the limited available data to propose ‘best resolution’ of current scientific insights into best clinical judgment and practice.

CHEMICAL PROPERTIES

See Table 1 and Figures 1–5.

Fluoxetine and fluvoxamine are phenylpropanolamines, sertraline is a naphthaleneamine, and citalopram is a racemic bicyclic naphthalene derivative (Emslie et al., 1999). In contrast to the TCAs, the SSRIs selectively block serotonin reuptake, with no effect on norepinephrine reuptake (Bergstrom et al., 1988). Paroxetine, citalopram, and sertraline are the most potent serotonin-reuptake inhibitors *in vitro*, whereas fluoxetine is the least potent serotonin-reuptake inhibitor (Emslie et al., 1999). The site of action of the SSRIs is believed to be the serotonin-reuptake pump as opposed to the neurotransmitter receptor site. Chemically, they are unrelated to the TCAs.

While sertraline can inhibit dopamine uptake more than the other SSRIs (Emslie et al., 1999), administration of other SSRIs (e.g., fluoxetine, citalopram, and paroxetine) has been associated with dopamine-blocking effects including extrapyramidal side effects, tardive dyskinesia, and akathisia (Bouchard et al., 1987; Lipinski et al., 1989; Tate, 1989). While direct evidence for dopamine-blocking effects of SSRIs such as paroxetine, fluoxetine, and citalopram are lacking, dopamine inhibition has been hypothesized to result via an indirect effect of serotonin (Korsgaard et al., 1985). Serotonin has been shown to inhibit dopamine neurons (Baldessarini and Marsh, 1990), and SSRIs reduce amphetamine-induced stereotypic behaviors and dystonia secondary to haloperidol administration in nonhuman primates (Korsgaard et al., 1985). The serotonin antagonist cyproheptadine does the reverse. Finally, Lipinski et al. (1989) have hypothesized that serotonergic inhibition of dopamine function results in akathisia in some patients treated with SSRIs. The clinical significance of more or less potent serotonin-reuptake inhibition, dopamine effects, etc., is unknown.

The SSRIs are metabolized primarily by the liver. Active and inactive metabolites are excreted in the urine by the kidneys. When administered at standard doses of 20 mg/day, fluoxetine achieves peak plasma levels after 6–8 hours. It has a longer elimination half-life than the other SSRIs and standard TCAs of 2–3 days after a single dose and 8 days after repeated administration (Emslie et al., 1999). Moreover, its primary active metabolite, norfluoxetine, has a half-life of 7–19 days. In fact, norfluoxetine is four times more potent than fluoxetine in inhibiting serotonin reuptake. Although it may take 6–8 weeks for steady-state

TABLE 1 Comparison of Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, and Citalopram Clinical Profiles

	Fluoxetine	Sertraline	Paroxetine	Fluvoxamine	Citalopram
Long half-life	Yes	No	No	No	No
Increases plasma levels of other psychotropic medications	Yes	No	No	No	No
Overall side effects	More	Less	Less	Less	Less
Increased anxiety and restlessness	More	Less	Less	Less	Less

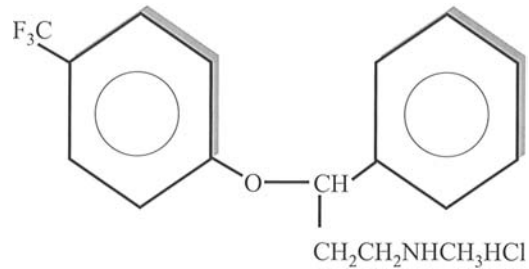


FIGURE 1 Molecular structure of fluoxetine.

plasma levels of fluoxetine to be achieved, once they occur they remain steady thereafter. Fluoxetine is highly protein bound (95%).

In contrast to fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram have inactive metabolites. Half-lives of these SSRIs range from 12 to 36 hours, and mean peak plasma concentrations occur between 4 and 9 hours in adults (Table 2). The half-life of sertraline is approximately 26 hours, the half-life of paroxetine is approximately 14 hours, the half-life of citalopram is approximately 35 hours, and the half-life of fluvoxamine is approximately 16 hours—considerably less than that of fluoxetine. Steady-state sertraline, fluvoxamine, and

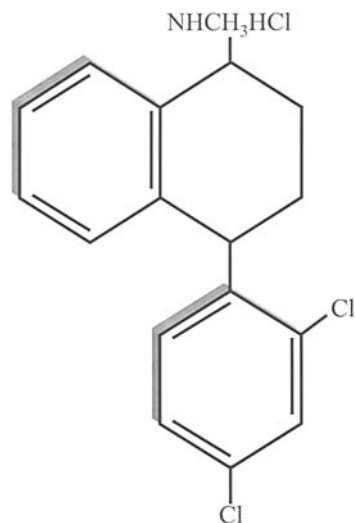


FIGURE 2 Molecular structure of sertraline.

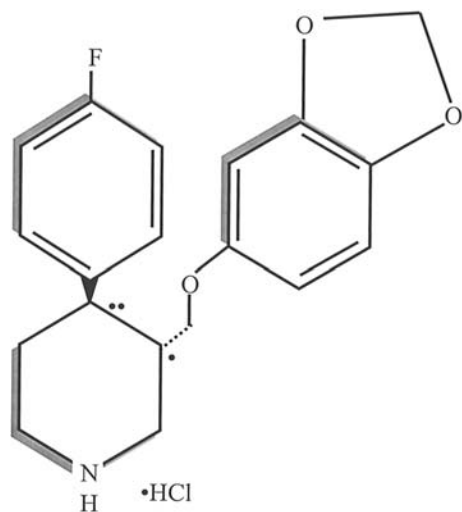


FIGURE 3 Molecular structure of paroxetine.

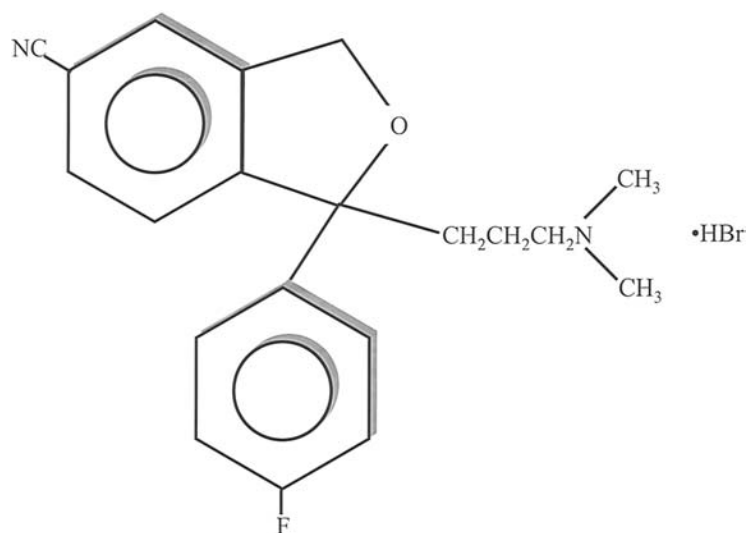


FIGURE 4 Molecular structure of citalopram.

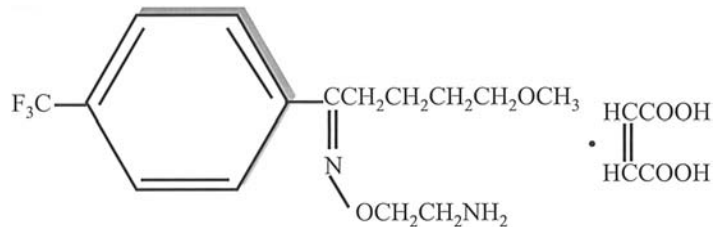


FIGURE 5 Molecular structure of fluvoxamine.

citalopram levels are generally achieved within one week of daily dosing, while steady-state paroxetine levels are attained within 10 days. It should be noted that there is marked variability among different individuals in steady-state levels of SSRIs that do not appear to be clinically relevant in adults (Emslie and Judge, 2000). It is currently not known whether variability in steady-state levels in children has potential clinical significance. Children may, however, take longer to become tolerant to a particular medication dose and increase in dose than adults. At steady state, the half-life of the SSRIs appears to be much lower in children. Axelson and colleagues studied the pharmacokinetics of sertraline and citalopram at doses of 50 and 20 mg/day, respectively, and found the half-lives to be 14–16 hours (presented at the American College of Neuropsychopharmacology 2000). Findling et al. (1999) found that the half-life of paroxetine 10 mg/day was 11.1 ± 5.2 hours. The half-life of sertraline when administered at 200 mg Q AM ranges from 6.9 to 8.6 hours (Tremaine et al., 1997).

Fluvoxamine, sertraline, paroxetine, and citalopram undergo extensive first-pass metabolism. In contrast to fluoxetine, their principal metabolites have been shown to be significantly less active than the parent compounds. Paroxetine and sertraline are highly protein bound (95–98%), whereas fluvoxamine and citalopram are less protein bound (80%).

Compared to fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram do not increase plasma levels of other psychotropic medications to the same extent (Berman et al., 1992). This may be particularly true of fluvoxamine because of its differential inhibition of the cytochrome P450 isoenzymes system in the liver by different SSRIs (DeVane, 1994; DeVane and Sallee, 1996; Leonard, 1996). There is very limited specific information in children on absorption, metabolism, SSRI plasma levels/therapeutic range, and potential drug interactions. Because of the increased liver: whole body ratio in children, higher mg/kg doses of SSRIs would likely be necessary to achieve plasma levels in children comparable to those observed in adults (Emslie et al., 1999). Substantial individual variability in steady-state fluoxetine + norfluoxetine plasma levels were observed in 40 children 12.2 ± 2.7 years who were administered fluoxetine 20 mg/day over

TABLE 2 Pharmacokinetics of Serotonin Reuptake in Children and Adolescents

Generic name (brand name)	Onset of action	Peak plasma concentration (hr)	Plasma half-life	Metabolism and excretion	Comments
Fluoxetine (Prozac)	Usually within 2–4 weeks	6–8	2–3 days, active me- tabolite norfluox- etine 7–9 days	Liver; active, and in- active metabolites excreted by kidney	May take up to 6–8 weeks or even 12 weeks for clinical response
Sertraline (Zoloft)	2–3 weeks	4.5–8.4	14–16 hours	Extensive first-pass metabolism	May take up to 6–8 weeks or even 12 weeks for clinical response
Paroxetine (Paxil)	2–3 weeks	3–8	14 hours	Extensive first-pass metabolism	May take up to 6–8 weeks or even 12 weeks for clinical response
Fluvoxamine (Luvox)	2–3 weeks	3–8	16 hours	Extensive first-pass metabolism	May take up to 6–8 weeks or even 12 weeks for clinical response
Citalopram (Celexa)	2–3 weeks	4	14–16 hours	Extensive first-pass metabolism	May take up to 6–8 weeks or even 12 weeks for clinical response

a 4-week period [mean 219.4 ± 120.17 ng/mL, range 15–540 ng/mL (Travis et al., 1993)]. Riddle et al. (1992) studied 10 children and adolescents with OCD on fixed-dose fluoxetine 20 mg/day for 8 weeks and one child on fluoxetine 20 mg/day for 4 weeks with mean fluoxetine + norfluoxetine levels of 322 ng/mL and substantial individual variability among individual subjects. These levels were somewhat higher than those observed by Travis and colleagues (1993). Treatment duration was longer (8 weeks vs. 4 weeks) in Riddle and associate's (1992) investigation so that levels may increase with longer acute treatment (Emslie et al., 1999).

More recently, a once-weekly, enteric-coated formulation of fluoxetine has been tested on adults with major depressive disorder and approved by the FDA. MDD patients who had responded well to fluoxetine 20 mg/day were randomized to a once-weekly dose of fluoxetine 90 mg, 20 mg/day of fluoxetine, or placebo for 25 weeks (Schmidt et al., 2000). Relapse rates were significantly lower in both treatment groups compared to placebo. Specifically, 50% of 122 patients on placebo relapsed vs. 26% of 189 patients on fluoxetine 20 mg/day and 37% of 190 patients on 90 mg fluoxetine per week. Relapse rates did not differ significantly between patients receiving weekly vs. daily fluoxetine. Gastrointestinal upset was significantly reduced in patients treated with the weekly preparation of fluoxetine compared to daily dose fluoxetine. This may be in part due to its 2-hour delay in peak plasma concentration as compared to standard preparation daily dose fluoxetine. There have been no published studies in children and adolescents, although they are clearly warranted, particularly if they might facilitate compliance and reduce problematic side effects.

It should be noted that Eli Lilly recently discontinued studies of the R-fluoxetine isomer initially believed to be a safer form of fluoxetine. This action resulted from a clinical trial demonstrating a statistically significant small increase in QTc prolongation in patients treated with high-dose R-fluoxetine (Mechcatie, 2000a). Although this prolongation in QTc is believed to be a clinically insignificant cardiac effect, Eli Lilly opted to discontinue further trials of the R-fluoxetine isomer (Psychiatric News, 2000a).

INDICATIONS

See Table 3.

Major Depressive Disorder

In adults, placebo-controlled studies have shown the efficacy of the SSRIs, fluoxetine, sertraline, paroxetine, and citalopram to be similar to that of TCAs (Benfield et al., 1986). These SSRIs are FDA approved for treating adult MDD. While

TABLE 3 Indications for SSRIs (Fluoxetine, Sertraline, Fluvoxamine, Paroxetine, and Citalopram) in Child and Adolescent Psychiatry

FDA-established indications:
OCD (Fluvoxamine and Sertraline)
Probable indications:
OCD (Fluvoxamine and Sertraline)
MDD
Social anxiety disorder
Selective mutism
Possible indications:
Dysthymia
Premenstrual dysphoric disorder
ADHD
Trichotillomania
Compulsive impulse control disorders
Anxiety/panic disorder
Anorexia nervosa (weight-recovered state only)
Bulimia nervosa
Prader-Willi syndrome
Self-injurious behavior
Borderline personality disorder
PTSD
Drug craving

fluvoxamine is not FDA approved for treating adults with MDD, it is routinely prescribed in clinical practice for MDD and is believed to be effective for this condition. The SSRIs have certain characteristics that make them especially attractive agents for use in children and adolescents. Specifically, impulsivity, suicidal behavior, and aggression have been associated with reduced cerebrospinal fluid (CSF) levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Traskman et al., 1981; Roy et al., 1989; Virkkunen et al., 1989; Mann et al., 1992).

Neuroendocrine studies of depressed adolescents suggest that abnormal CNS serotonin function may be present (Kutcher et al., 1991). SSRIs that increase CNS serotonin levels may, therefore, be particularly beneficial in this population (Ryan et al., 1988; Kutcher et al., 1991). Depression in children and adolescents is frequently characterized by impulsivity and comorbid disruptive behavior disorders, so that SSRIs may be attractive to clinicians because they increase CNS serotonin levels, and hence may reduce impulsivity.

Open-label trials and retrospective chart reviews of SSRIs including fluoxetine (Joshi et al., 1989; Jain et al., 1992; Kutcher et al., 1994; Ghaziuddin et al., 1995), paroxetine (Rey-Sanchez and Gutierrez-Casares, 1997), fluvoxamine (Apter et al., 1994), and sertraline (Tierney et al., 1995; McConville et al., 1996; Ambrosini et al., 1999) in child and adolescent MDD have reported response rates of 65–75%.

Simeon et al. (1990a) conducted a double-blind, placebo-controlled study of fluoxetine in 40 adolescent MDD patients 13–18 years of age. Moderate to marked improvement was observed in two thirds of patients, with significant improvement noted by 3 weeks of treatment with both fluoxetine and placebo. There were no significant group differences, although there was a nonsignificant trend toward fluoxetine superiority in reducing depressive symptoms. The information provided by the investigators precludes their inclusion in subsequent meta-analyses (Ryan and Varma, 1998).

Emslie et al. (1997) conducted a double-blind, placebo-controlled study of 8-week fixed-dose 20 mg/day fluoxetine or placebo in 96 child and adolescent outpatients with MDD 7–17 years of age. Weekly assessments were performed. Twenty-seven of 48 subjects (56%) treated with fluoxetine were rated as very much improved, whereas only 16 of 48 (33%) were rated as very much improved on placebo. Significant differences in reduction in MDD symptom severity were observed between fluoxetine 20 mg/day and placebo by 5 weeks of treatment. These response rates were comparable to those observed in adult MDD patients.

Schweizer and associates (1992) found that in adult MDD patients, daily 20 mg doses of fluoxetine were as effective as 60–80 mg/day in achieving improvement in depressive symptoms and that little was gained by raising the daily dose of fluoxetine above 20mg. They did note that a trial of six to eight weeks may be required before resistance to fluoxetine treatment is inferred. A multicenter, double-blind, placebo-controlled study sponsored by Eli Lilly recently compared flexible dosage fluoxetine treatment (20–60mg/day) vs. placebo. The results of this study have not yet been made available, although Emslie reported that fluoxetine was superior to placebo in pediatric MDD patients at the American College of Neuropsychopharmacology meeting, December 2000, and the American Psychiatric Association Meeting, May 2001. Moreover, a multicenter National Institute of Mental Health–funded investigation, “Treatment for Adolescents with Depression Study (TADS) (John March, M.D., MPH, Duke University, principal investigator) will study 432 adolescents 12–17 years old comparing fluoxetine alone (20–60mg/day), cognitive behavioral therapy alone (CBT), both fluoxetine and cognitive behavioral therapy (combination therapy) and a placebo control condition. It should be noted that while these studies use a starting dose of fluoxetine 10mg/day, they require that the dose be increased to a minimum of 20 mg/day. Recent investigation in adults has suggested that some MDD patients may respond to lower doses of fluoxetine (e.g., 5 or 10 mg/

day). Further study of smaller doses of fluoxetine is clearly warranted in children and adolescents.

More recently, a multicenter, randomized, double-blind, placebo-controlled study sponsored by SmithKline Beecham compared paroxetine, imipramine, and placebo in 270 pediatric MDD patients (Keller et al., 2001). Paroxetine was found to be significantly superior to both placebo and imipramine in the MDD patients, with no significant difference observed between imipramine and placebo. The results of this study have led many experts and clinicians alike to conclude that the TCAs are not likely to be effective in pediatric MDD and that their side effect profile limits the likelihood and rationale for additional study of TCAs in children and adolescents with MDD (Ryan & Varma, 1998). It should be noted that another large, unpublished study found comparable effects of paroxetine and placebo in adolescents with unipolar MDD (Milin et al., 1999).

Another multicenter double-blind, placebo-controlled study of sertraline in the treatment of children and adolescents with MDD (6–17 years of age) has recently been completed, and the results are pending. Forest Pharmaceuticals, Inc. and Parke-Davis also recently completed a double-blind, placebo-controlled study of citalopram in the treatment of children and adolescents with MDD. These results are also pending. There have been no controlled studies of fluvoxamine in pediatric MDD patients, nor are any, to our knowledge, planned. It should be noted that SmithKline Beecham conducted a double-blind, placebo-controlled study of paroxetine in Europe and Canada in adolescents with MDD. This study found no significant difference between paroxetine and placebo. The data from this study has not been published.

At the December 2000 meeting of the American College of Neuropsychopharmacology, Thase (unpublished data) compared remission rates with venlafaxine, a nonselective serotonin-reuptake inhibitor (see Chapter 10) as compared to SSRIs in adults with MDD. Mega- and meta-analyses of 17 randomized double-blind trials from 2095 patients were analyzed. Remission rates were significantly greater in patients treated with venlafaxine (45%; 382 of 851 patients) than in patients treated with the SSRIs (35%; 260 of 748 patients) or placebo (25%; 110 of 446 patients). This was particularly true for venlafaxine doses of 150 mg/day or greater. By 2-weeks of treatment, a significant difference in remission of depressive symptoms was observed between venlafaxine and the SSRIs. In contrast, SSRI-placebo differences in symptom remission were not noted until 4 weeks of treatment. These results suggested further that, compared to SSRI treatment, one additional patient per 10 treated cases would experience remission of symptoms if venlafaxine were used as first-line treatment (see Chapter 10). A recent multicenter double-blind, placebo-controlled study of sustained release venlafaxine XR in pediatric MDD patients, 7–17 years, was recently completed. It is unknown whether remission rates might differ in pediatric MDD patients treated with SSRIs vs. venlafaxine. Further study is clearly warranted.

Obsessive-Compulsive Disorder

While OCD was once thought to be a rare condition, it is now recognized as a severe and highly prevalent condition that affects 1–3% of the world's population (Rasmussen and Eisen, 1994). Its lifetime prevalence in childhood and adolescence is comparable to that of diabetes and asthma and ranges from 2–3% (Flament et al., 1988; Valleni-Basile et al., 1994; Hanna, 1995). As many as 80% of all cases of OCD have their onset in childhood and adolescence (Pauls et al., 1995; Nestadt et al., 2000). Development of effective treatments for the condition during childhood and adolescence is, therefore, critical, particularly since medication-refractory patients may be more likely to have earlier onset of OCD symptoms (Blanes and McGuire, 1997). Functional neuroimaging studies in adult OCD patients with childhood onset of illness have demonstrated increased metabolic abnormalities in ventral prefrontal-striatal-thalamic circuitry associated with OCD symptom severity and treatment response (Swedo et al., 1992; Saxena et al., 1998). These findings, among others, have resulted in the emergence of a neurodevelopmental model for OCD (Rosenberg and Keshavan, 1998).

Pharmacological studies in adults and children with OCD provide compelling evidence for a critical serotonergic role in OCD. Medications that inhibit serotonin reuptake have repeatedly been shown to be effective in reducing OCD symptomatology, whereas medications that inhibit norepinephrine reuptake are ineffective (Leonard et al., 1988; Leonard et al., 1989; Flament et al., 1990; Leonard et al., 1991). As described in Chapter 8, clomipramine was the first serotonin-reuptake inhibitor (nonselective as it also inhibits norepinephrine reuptake) found to be effective in pediatric OCD. Recent investigation in adult OCD patients demonstrating comparable efficacy and reduced side effects of the SSRIs such as fluoxetine, sertraline, and fluvoxamine as compared to clomipramine (Grados et al., 1999) have resulted in intense investigation into the efficacy and safety of the SSRIs in pediatric OCD.

Apter et al. (1994) treated 20 adolescent inpatients 13–18 years of age with OCD or depression in an 8-week open-label trial of fluvoxamine using doses of 100–300 mg/day. Fluvoxamine was most effective in OCD patients, with an overall 29.3% decrease in OCD symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale. More recently, a multicenter (17 centers), double-blind, placebo-controlled study in 8- to 17-year-old children and adolescents with OCD sponsored by Solvay Pharmaceuticals demonstrated fluvoxamine (50–200 mg/day) to be superior to placebo in reducing OCD symptom severity (Riddle et al., 1996, 2001). Fluvoxamine was superior to placebo at weeks 1, 2, 3, 4, 5, 6, and 10. This resulted in its being the first SSRI to be FDA approved for use in children and adolescents with OCD.

While fluvoxamine (and other SSRI) plasma levels do not appear to be correlated with clinical response or side effects (Grados et al., 1999), recent inves-

tigation of fluoxetine and fluvoxamine levels in brain of OCD patients using a magnetic resonance imaging (MRI) technique called proton magnetic resonance spectroscopy (1-H MRS) and in plasma has found increased brain levels of fluoxetine and fluvoxamine in brain as compared to plasma (Strauss et al., 1997). Moreover, steady-state brain concentrations of fluvoxamine were achieved more rapidly (30 days) than with fluoxetine.

Subsequent investigation to determine the long-term (12 month) efficacy and safety of fluvoxamine in 99 children and adolescents 8–17 years of age with OCD was conducted (Walkup et al., 1998). After the first 3 weeks of treatment, fluvoxamine dosages were increased in all patients to 200 mg/day. Significant reduction in OCD symptom severity was seen with chronic treatment, and this improvement was maintained during treatment with fluvoxamine. Treatment with fluvoxamine was also found to be safe with relatively few side effects. An overall 42% reduction in OCD symptom severity was seen at the end of the 12-month trial and only 11 of the 99 children withdrew because of side effects and 3 because of lack of efficacy of fluvoxamine. Moreover, pediatric OCD patients who improved after acute 10-week treatment during the randomized controlled trial of fluvoxamine vs. placebo (Riddle et al., 1996) demonstrated additional benefit during long-term treatment (mean additional reduction in OCD symptom severity of 31%). Thus, additional improvement with longer-term SSRI treatment may be achieved in pediatric OCD patients with relatively few side effects. Thus, future studies of SSRIs in pediatric OCD patients should measure chronic as well as acute effects of SSRIs.

Fluvoxamine was recently approved by the FDA for “pediatric exclusively” and was the first SSRI to achieve this classification (Psychiatric News, 2000b). Fluvoxamine at doses up to 300 mg/day was demonstrated to be effective in treating OCD in patients 8 and older. By achieving “pediatric exclusivity,” fluvoxamine’s patent protection was extended for an additional 6 months.

A subsequent multicenter, double-blind, placebo-controlled investigation in children and adolescents with OCD sponsored by Pfizer Incorporated found sertraline to be superior to placebo (March et al., 1998). Of the 187 pediatric OCD patients treated in this study, 53% of subjects treated with sertraline experienced at least a 25% reduction in OCD symptom severity as compared to 37% of patients treated with placebo. Sertraline was well tolerated with relatively few side effects. March and colleagues (1998) then treated 137 pediatric OCD patients 6–18 years of age with sertraline 50–200 mg/day (mean dose 120 mg \pm 80 mg) for 12 months. As with long-term fluvoxamine treatment, continued sertraline treatment resulted in additional marked improvement in OCD symptom severity. Only 12% of patients had to discontinue taking sertraline because of problematic side effects. The most commonly observed side effect was hyperkinesia, noted in 4 of the 137 patients.

Open-label investigation of fluoxetine in the treatment of children and ado-

lescents with OCD suggested possible efficacy for the condition (Liebowitz et al., 1990; Geller et al., 1995). A double-blind, placebo-controlled study in 14 children and adolescents with OCD found fluoxetine to be superior to placebo in reducing OCD symptom severity (by 44%) (Riddle et al., 1992). A multicenter, double-blind, placebo-controlled study of fluoxetine (20–60 mg/day) sponsored by Eli Lilly was recently completed. The results of the study are not known at present. There have been no long-term treatment studies of fluoxetine in pediatric OCD. These are clearly warranted as a further decrease in OCD symptoms with relatively few side effects can be achieved with long-term treatment (Thomsen and Leckman, 2000).

Rosenberg et al. (1999) conducted a 12-week, open-label study of paroxetine in 20 pediatric OCD patients 8–17 years of age to evaluate its safety and effectiveness. Paroxetine proved safe and effective in pediatric OCD patients, who exhibited a mean 29.4% decrease in OCD symptom severity after 12 weeks of paroxetine treatment. Hyperactivity, behavioral activation, headache, insomnia, nausea, and anxiety were the most common side effects but did not result in medication discontinuation although medication dosage was reduced in three patients. Side effects were more common in patients under 10 years of age. A multicenter, double-blind, placebo-controlled study of paroxetine (10–60 mg/day) in pediatric OCD patients was recently completed. This investigation demonstrated that paroxetine was safe and effective in treating pediatric patients, 8–17 years of age, with paroxetine (Emslie et al., 2000). One hundred and sixty-seven children (8–11 years) and 168 adolescents (12–17 years) were studied. Responders ($\geq 25\%$ decrease in OCD symptom severity) to an initial 16-week open-label paroxetine flexible dosage trial (10–60 mg/day) were then randomized to either continue paroxetine or to placebo under double-blind conditions for 16 weeks. Nonresponders during the open-label 16-week treatment course were not randomized and were offered alternative treatment. Significantly more patients randomized to paroxetine vs. placebo in the double-blind trial exhibited an additional $\geq 25\%$ decrease in OCD symptom severity (28.9% for paroxetine vs. 14.4% for placebo). In the double-blind treatment phase, significantly more patients randomized to placebo than medication exhibited worsening of their OCD symptoms. Fewer patients randomized to paroxetine (34.7%) vs. placebo (43.9%) relapsed, although this difference was not statistically significant. The medication was generally well tolerated with few side effects. The most common side effects resulting in medication discontinuation were hostility (approximately 3%), hyperactivity (2%), and agitation (approximately 2%). Several adverse events were noted to be more frequent in younger children than in adolescents, including agitation (11.4% vs. 3.6%), hyperactivity (14.4% vs. 8.3%), trauma (18.6% vs. 8.3%), infection (12% vs. 7.1%), manic reaction (4.2% vs. 0.6%), and myoclonus (9.6% vs. 4.8%).

Recent neuroimaging studies in treatment-naïve, pediatric OCD patients have begun to identify potential neurobiologic markers that may predict response to paroxetine (or lack thereof) in pediatric OCD patients. Volumetric magnetic resonance imaging (MRI) and computerized tomography (CT) studies in pediatric OCD patients measuring brain structure and size have identified localized abnormalities in ventral prefrontal cortex (Rosenberg and Keshavan, 1998), the striatum (Rosenberg et al., 1997; Luxenberg et al., 1988) and the thalamus (Gilbert et al., 2000) associated with OCD symptom severity with no abnormalities in total brain volume.

Gilbert et al. (2000) found that thalamic volume was significantly increased in nondepressed, treatment-naïve pediatric OCD patients as compared to age- and sex-matched healthy comparison subjects. A differential maturation in thalamic volume was observed in OCD patients as compared to controls so that larger thalamic volumes were seen in younger OCD patients as compared to controls. This suggested a possible critical period of aberrant maturation of thalamus in OCD patients as compared to controls with potential treatment implications. Remarkably, after 12 weeks of paroxetine therapy, thalamic volumes decreased significantly to levels comparable to those observed in healthy children. Decrease in thalamic volume was positively correlated with reduction in OCD symptom severity so that larger thalamic volumes before treatment in pediatric OCD patients predicted better response to paroxetine, whereas smaller pretreatment thalamic volumes in OCD patients predicted poorer response to paroxetine treatment. These findings suggested that abnormalities in serotonin neurotransmission could result in volumetric abnormalities in the thalamus that may be reversible with effective paroxetine treatment.

No differences in the size of the thalamus were observed in adult OCD patients compared to adult controls (Jenike et al., 1996), which may reflect the differential maturation of the thalamus in pediatric OCD patients as compared to healthy children. Younger OCD patients had larger thalamic volumes than did controls until approximately 16–17 years of age when control volumes appear to ‘catch-up’ with volumes in OCD patients). In addition, most of the adult OCD patients studied by Jenike and colleagues (1996) had been treated with SSRI medication. The findings of Gilbert and colleagues (2000) suggest that SSRI treatment may alter the size of the thalamus and thereby eliminate case-control differences in thalamic volume.

Using another brain imaging technique, proton magnetic resonance spectroscopy (1-H MRS), which allows for the noninvasive measurement of brain chemistry without putative ionizing radiation risks, Fitzgerald and colleagues (2000) identified localized functional neurochemical marker abnormalities in medial but not lateral thalamus (Figs. 6, 7). The medial thalamus, particularly the dorsomedial nucleus of the thalamus, has been especially implicated in the patho-

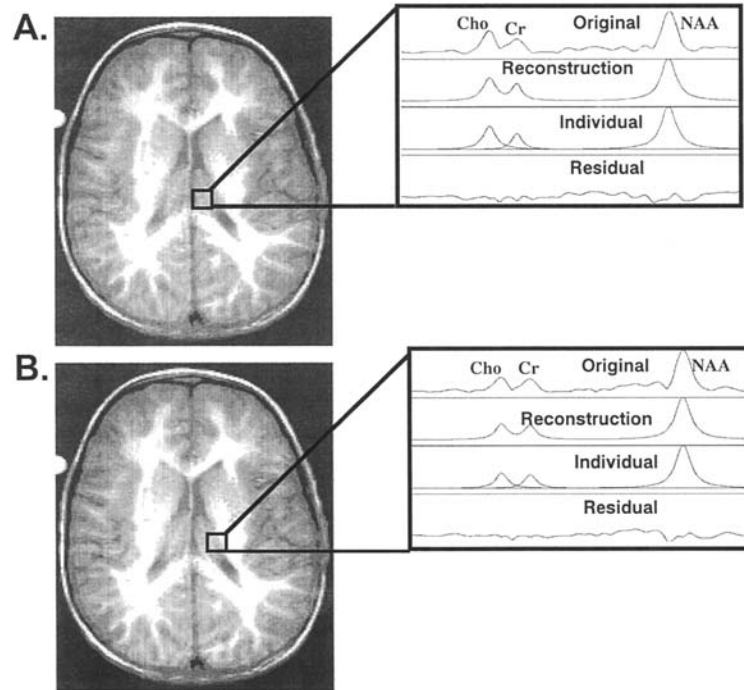


FIGURE 6 Sample spectra for voxels placed in the left medial thalamus (A) and left lateral thalamus (B). Individual peaks for choline compounds (Cho), creatine/phosphocreatine (Cr), and *N*-acetyl-aspartate (NAA) were resolved from the original spectrum (top), leaving a residual (bottom). (From Fitzgerald et al., 2000.)

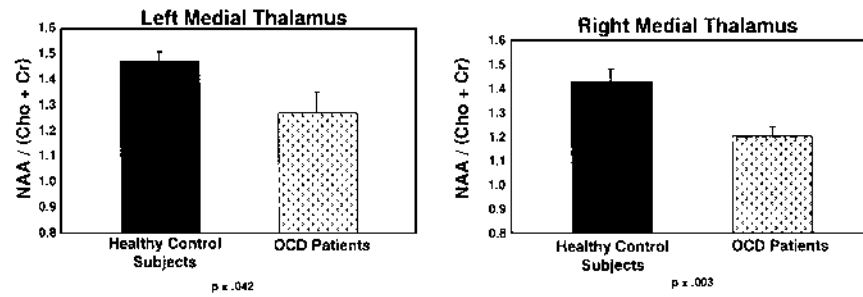


FIGURE 7 Left and right NAA/(Cho + Cr) metabolite ratios by group. (Adapted from Fitzgerald et al., 2000.)

genesis of OCD (Modell et al., 1989). Compounds that can be measured by 1-H MRS include the putative neuronal marker, *N*-acetyl-aspartate (NAA) (Birken and Oldendorf, 1989; Urenjak et al., 1992; Michaelis et al., 1993; Ebisu et al., 1994). Fitzgerald et al. (2000) observed significant reductions in NAA levels suggestive of neuronal dysfunction in medial but not lateral thalamus (Fig. 6). NAA has been shown to be localized to the neurons of the brain (Urenjak et al., 1992) and is reduced in diseases associated with neuronal loss and dysfunction including Alzheimer's disease (MacKay et al., 1996). Increased thalamic volumes in pediatric OCD patients were associated with reduced NAA levels suggestive of neuronal dysfunction.

Reduced medial thalamic NAA levels in pediatric OCD patients were hypothesized to result from excess activity of glutamatergic afferents projecting to the thalamus from ventral prefrontal-striatal circuitry (Fitzgerald et al., 2000). Excess glutamatergic concentrations can be neurotoxic, and functional neuroimaging studies in OCD patients (Rauch et al., 1994; Breiter et al., 1996) have demonstrated increased thalamic activity when OCD symptoms are provoked which suggests increased glutamatergic projection to the thalamus (Alexander et al., 1990; Salt and Eaton, 1996) (Fig. 8).

Rosenberg and Keshavan (1998) had hypothesized that glutamatergic abnormalities modulating serotonin neurotransmission may be involved in the pathogenesis of OCD. This was suggested by the fact that the caudate nucleus, a primary locus of abnormality in OCD (Rauch et al., 1998), receives a very dense glutamatergic innervation from ventral prefrontal cortex (Becquet et al., 1990; Parent et al., 1995; Parent and Hazrati, 1995). Ablation of frontal cortical regions results in a marked decrease in caudate glutamate concentrations (Kim et al., 1977; Calabresi et al., 1996). Glutamate has also been shown to inhibit the presynaptic release of serotonin *in vivo* (Reisine et al., 1982; Becquet et al., 1990). Serotonergic neurons also exert a prominent influence on caudate glutamatergic neurons since the caudate nucleus receives a dense serotonin innervation from the dorsal raphe nucleus cell bodies (Greybiel and Ragsdale, 1983; Smith and Parent, 1986).

Using 1-H MRS, Rosenberg et al. (2000) observed significantly elevated caudate glutamatergic concentrations in treatment-naïve pediatric OCD patients as compared to age- and sex-matched healthy children (Figs. 9, 10). Caudate glutamatergic concentrations decreased dramatically after 12 weeks of paroxetine therapy to concentrations comparable to those observed in healthy children. Reduction in caudate glutamatergic concentrations was robustly correlated with reduction in OCD symptom severity so that increased pretreatment caudate glutamatergic concentrations in pediatric OCD patients predicted better response to paroxetine therapy (Fig. 11). Conversely, lower pretreatment caudate glutamatergic concentrations predicted poorer response to paroxetine therapy. It should be noted that these glutamatergic abnormalities appeared to be localized

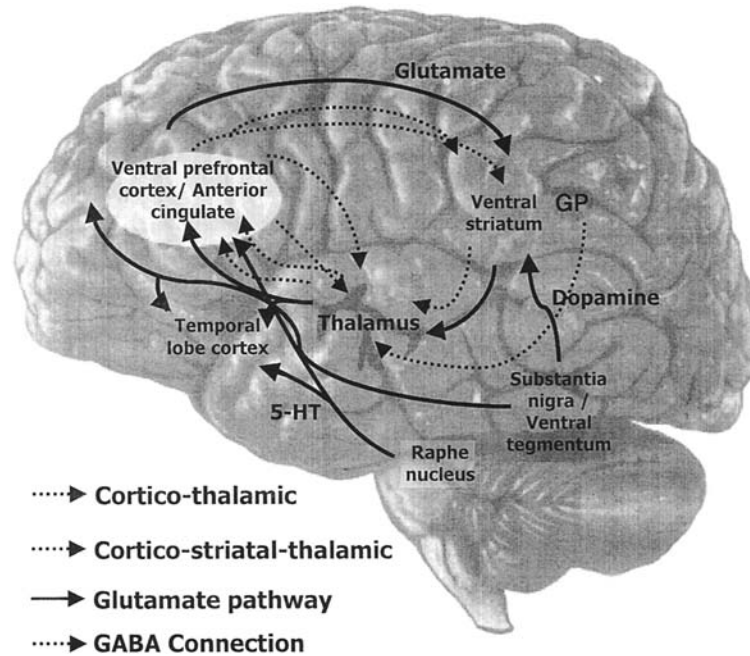


FIGURE 8 Illustration of cortico-striato-thalamo-cortico network in obsessive-compulsive disorder. Neurotransmitters: Glu, Glutamate; GABA, gamma-amino-butyrac acid; DA, dopamine; 5-HT, serotonin. Brain regions: VPFC, ventral prefrontal cortex; AC, anterior cingulate; VS, ventral striatum; Thal, thalamus; TLC, temporal lobe cortex; RN, raphe nucleus; SN, substantia nigra; VT, ventral tegmentum. (Adapted from Rosenberg and Keshavan, 1998.)

to the caudate nucleus as no significant differences were observed in occipital glutamatergic concentrations between OCD patients and controls, nor did occipital glutamatergic concentrations decrease after paroxetine therapy (Rosenberg et al., 2000). Taken together, these studies underscore the potential clinical relevance of translating advances in developmental neuroscience into treatment development. Treatment studies performed in conjunction with neurobiological (e.g., neuroimaging) studies may result in the identification of neurobiological markers that help predict response to treatment (or lack thereof), which may result in enhanced diagnostic assessment and treatment of OCD. Preliminary investigation in pediatric OCD patients (Rosenberg and Keshavan, 1998; Rosenberg et al., 2000; Fitzgerald et al., 2000; Gilbert et al., 2000) suggests a reversible (with paroxetine) glutamatergically mediated thalamocortical-striatal dysfunction subtype of pediatric OCD.

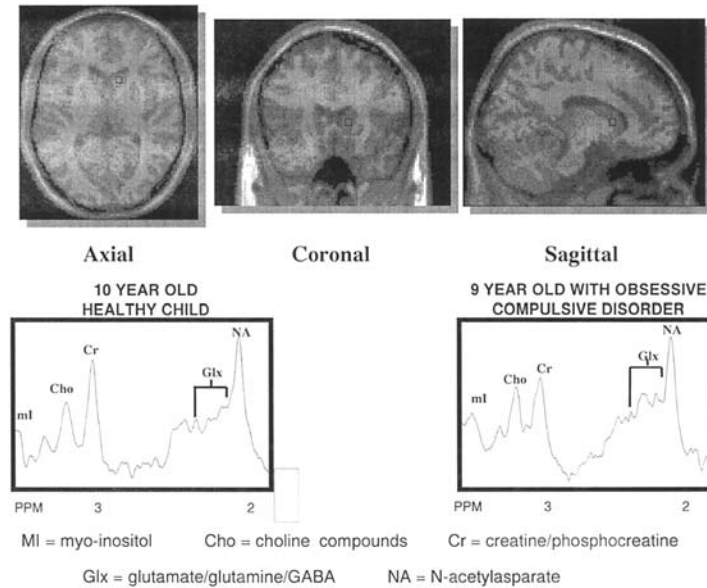


FIGURE 9 Illustration of voxel placement in left caudate nucleus. 1-H MRS of a 0.7 mL volume of interest centered in the left caudate in a 10-year-old healthy control and a 9-year-old treatment-naïve patient with obsessive-compulsive disorder as shown on the T1-weighted MR images. MI, Myoinositol; Cho, choline compounds; Cr, creatine/phosphocreatine; Glx, glutamate/glutamine/GABA; NA, N-acetylaspartate. (Adapted from Rosenberg et al., 2000.)

An open-label study of citalopram 20–60 mg/day in 22 adult OCD patients resulted in 76% of patients experiencing a 50% decrease in OCD symptom severity (Koponen et al., 1997). More recent double-blind, placebo-controlled investigation of citalopram at doses of 20, 40, and 60 mg/day in adult OCD patients demonstrated the medication to be effective and well tolerated (Montgomery et al., 2000). A 10-week open-label study of 23 children and adolescents with OCD suggested that citalopram 10–40 mg/day may be effective and well tolerated in pediatric OCD patients (Thomsen, 1997). Eleven subjects (47.8%) achieved at least a 30% reduction in OCD symptom severity, while seven patients responded but did not achieve a 30% reduction in OCD symptom severity and five patients experienced little or no improvement with citalopram treatment. The medication was well tolerated with relatively few side effects. Long-term open-label citalopram treatment for at least 2 years was then monitored in 28 pediatric OCD patients 13–19 years of age (Thomsen et al., 2000). Patients were treated with citalopram 40 mg/day for 10 weeks and then monitored over the rest of the 2-

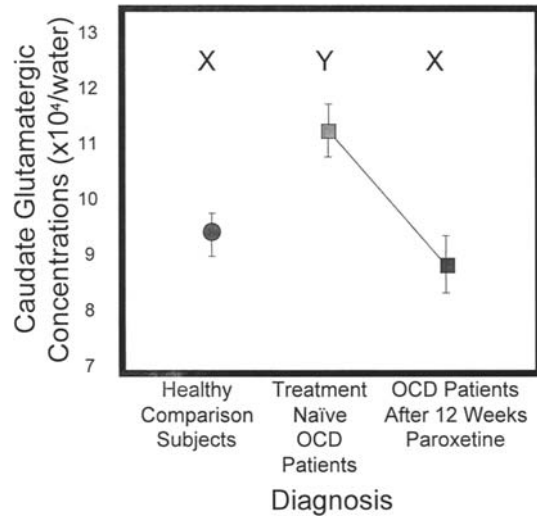


FIGURE 10 Caudate glutamatergic concentration by diagnostic and treatment condition. Groups not sharing the same letter are significantly different at $p < 0.05$. (Reprinted from Rosenberg et al., 2000.)

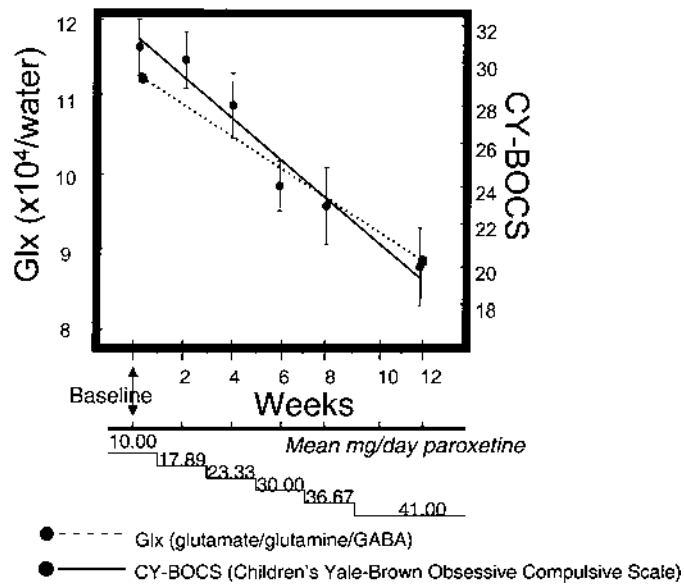


FIGURE 11 Left caudate glutamatergic concentrations versus obsessive-compulsive symptom severity as measured by the Children's Yale-Brown–Obsessive-Compulsive-Scale versus paroxetine dosage. (Reprinted from Rosenberg and Hanna, 2000.)

year period on a variable dose (range 40–60 mg/day). OCD symptoms decreased an additional 35% after at least 6 months of treatment with citalopram. Relatively few side effects were noted. It should be noted, however, that four of the OCD patients in the study suffered from persistent sedation and sexual dysfunction during the entire treatment period. There have been no double-blind, placebo-controlled studies of citalopram in pediatric OCD. Such studies are warranted to better delineate the role of citalopram in the treatment of pediatric OCD patients.

Parents and clinicians alike are still often confounded by the question of how long a child with OCD should remain on the SSRI. Recurrence of OCD symptoms is common, and typically the illness does not spontaneously resolve (Thomsen and Leckman, 2000). Nonetheless, long-term follow-up studies of pediatric OCD patients has shown that 20–30% of patients exhibit complete remission of symptoms with full recovery (Leonard et al., 1993; Thomsen, 1994). Thus, the current standard of care advocates tapering and discontinuing medication treatment after 1–1½ years of effective treatment with remission of symptoms (Thomsen and Leckman, 2000). It should be noted that this period is best defined as that dose at which the OCD symptoms are sufficiently alleviated and not necessarily when treatment is commenced. For example, if fluoxetine is initiated at 10 mg/day and resolution of symptoms is noted at 8 weeks of treatment, the 1- to 1½-year period should be initiated at this point rather than when the medication was first administered.

TREATMENT-REFRACTORY OCD PATIENTS

It should be noted that medication response in pediatric OCD patients typically ranges from 20 to 45%, although additional symptom reduction may be observed with longer-term (e.g., 12 month) therapy. Goodman et al. (1992) noted that at least one third of OCD patients do not respond at all to adequate SSRI trials, and many responders do so only partially. Medication-refractory patients are also more likely to have early onset of illness (Blanes and McGuire, 1997). Current treatment guidelines advocate switching to another SSRI if an initial SSRI trial is insufficiently effective (Bernstein and Shaw, 1997). Many authorities advocate at least two or three SSRI trials before medication augmentation strategies. Failure of one SSRI does not mean that a patient will not respond to another SSRI (Grados et al., 1999). This necessitates tapering and discontinuing the initial SSRI before initiating the new SSRI. Cognitive behavioral therapy has also been shown to be an effective treatment in pediatric OCD (Liebowitz et al., 1990) and is sometimes effective as monotherapy in OCD. Certainly, before addition of an additional medication to an SSRI regimen is considered, an adequate trial of cognitive behavioral therapy is warranted. Nonetheless, monodrug therapy is simply not viable for all children with OCD. In addition, some patients who do not

experience complete response but who do not show significant improvement may be reluctant to discontinue their current SSRI regimen since there is no guarantee they will respond to another SSRI and they may lose the benefit they have already achieved. Therefore, close consultation with the parents and families with a complete risk-benefit analysis is indicated. Whether or not to add an SSRI to an existing SSRI regimen necessitates an individual case-by-case analysis.

In adult OCD patients, double-blind, placebo-controlled studies adding medications to serotonin-reuptake inhibitors that increase serotonin function including lithium and thyroid hormone (Pigott et al., 1991), buspirone (Pigott et al., 1992a), trazodone (Pigott et al., 1992b), and clonazepam (Pigott et al., 1992c) have not demonstrated superiority of active medication vs. placebo. McDougle and associates (1990, 1994) have shown that the addition of haloperidol (6.2 ± 3 mg/day) to the SSRI fluvoxamine is more effective than placebo in treatment-refractory OCD patients. This positive effect, however, was only observed in OCD patients with coexistent chronic tic disorders such as Tourette's syndrome. Addition of the dopamine antagonist pimozide has also been shown to be superior to the addition of placebo in OCD patients with either comorbid chronic tic disorders or schizotypal personality disorder (McDougle et al., 1990). These neuroleptics can have significant and potentially irreversible side effects, including tardive dyskinesia, limiting their routine use and necessitating the identification of safer augmentation strategies.

Open-label studies adding the atypical antipsychotic medications risperidone and olanzapine to SSRI regimens have been reported to be effective in reducing OCD symptom severity in adult OCD patients who have not responded sufficiently to monodrug therapy with serotonin-reuptake inhibitors (Jacobsen, 1995; Ravizza et al., 1996; Saxena et al., 1996; Stein et al., 1997; McDougle et al., 1998; Weiss et al., 1999).

Recently, McDougle and colleagues (2000) conducted a double-blind, placebo-controlled study of risperidone augmentation in adult OCD patients refractory to monodrug therapy with a serotonin-reuptake inhibitor. They studied 70 patients with OCD who were treated for 12 weeks in open-label fashion with a serotonin-reuptake inhibitor. Over 50% (36) proved refractory to SRI treatment and were randomized to be treated with 6 weeks of risperidone ($n = 20$) and 6 weeks of placebo ($n = 16$) augmentation. Fifty percent ($n = 18$) of risperidone-treated patients exhibited marked reductions in OCD symptom severity at mean daily doses of 2.2 ± 0.7 mg/day vs. 0% ($n = 0$) of patients in whom placebo was added to the serotonin reuptake inhibitor. Particularly noteworthy was the fact that risperidone augmentation was equally effective in OCD patients with and without comorbid tic disorders or schizotypal personality disorder. Risperidone augmentation was well tolerated with relatively few side effects. The most common side effect was transient sedation. The authors emphasized that risperidone

augmentation doses were considerably lower than those used to treat psychotic disorders (see Chapter 12).

There have been no placebo-controlled studies of medication-augmentation strategies in pediatric OCD patients refractory to SSRI monotherapy. Fitzgerald et al. (1999) reported effective risperidone augmentation of treatment with serotonin-reuptake inhibitors in four pediatric OCD patients who had responded insufficiently to monodrug therapy with a serotonin-reuptake inhibitor. Two of the patients had comorbid tic disorders, and three exhibited aggressive behavior or had violent obsessive images. Risperidone was effective in patients with and without comorbid tic disorders and was especially effective in patients with comorbid aggression and violent obsessive images. Low doses of risperidone augmentation not exceeding 1.5 mg/day were used. Doses were started at 0.25 mg/day and titrated in 0.25 mg increments no more rapidly than every 1–2 weeks.

Simeon et al. (1990b) treated six adolescent OCD patients who had failed to respond to monodrug therapy with clomipramine (mean doses 92 mg/day) for 3–32 weeks. Fluoxetine 20–40 mg/day was added, while clomipramine dosage was decreased. Marked improvement was observed in five of the patients, and moderate improvement was seen in one patient after 2–6 months of fluoxetine-clomipramine combination therapy. These effects persisted for up to 11 months. The authors noted that combination therapy resulted in better response at lower doses of both fluoxetine and clomipramine with fewer side effects.

Figuroa et al. (1998) extended this finding in their open-label case series of seven pediatric OCD patients treated with clomipramine-fluoxetine, clomipramine-sertraline, clomipramine-fluvoxamine, and clomipramine-paroxetine combinations. Treatment effects persisted up to 22 months after follow-up from the initiation of combination therapy. All patients benefited from the regimen. However, problematic cardiac side effects were observed in five of the seven patients. These were, in fact, the most common side effects. QTc prolongation was observed in two of the patients, and two also had tachycardia while on clomipramine-SSRI combination therapy. Other potential risks not observed in this sample could include manic switch, serotonin syndrome, insomnia or hypersomnia and headaches, extrapyramidal side effects or sexual dysfunction. Given the efficacy of risperidone and other atypical neuroleptic therapy, clomipramine should not be considered first-line augmentation therapy, particularly given the risks of exacerbating TCA side effects. If such therapy is commenced, it is critical to monitor EKGs, clomipramine plasma blood levels, and vital signs since SSRIs can increase clomipramine blood levels and/or its active metabolite, desmethyl-clomipramine. Clomipramine also inhibits serotonin reuptake more efficiently than does desmethylclomipramine, its active metabolite. Thus, the addition of other SSRIs to clomipramine therapy may help increase clomipramine levels in treatment-refractory patients. Fluoxetine may be particularly likely to increase

clomipramine blood levels and potentially increase cardiac and other TCA side effects, whereas fluvoxamine may do so to a lesser extent since it is the only SSRI that does not exhibit enzymatic inhibition at the cytochrome P450 2D6 site (Table 4). However, close monitoring is recommended for all clomipramine-SSRI combinations. SSRI-clomipramine combinations may, however, reduce the seizure threshold (Szegedi et al., 1996). Clomipramine could also increase SSRI absorption or protein binding. Thus, although SSRI-clomipramine combination therapy was more effective than monotherapy in all seven patients studied by Figueroa and colleagues (1998), close monitoring is indicated whenever this combination is implemented.

Clomipramine also inhibits serotonin reuptake more efficiently than does desmethylclomipramine, its active metabolite, so fluvoxamine addition to clomipramine therapy has been utilized to increase clomipramine levels in treatment-refractory patients (Grados et al., 1999). Augmenting clomipramine (and many other medications) with fluvoxamine has been hypothesized to be safer than with other SSRIs, particularly fluoxetine.

Open case series adding buspirone (Alessi and Bos, 1991; Thomsen and Mikkelsen, 1999) and clonazepam (Leonard et al., 1994) to patients who have not responded sufficiently to SSRI monotherapy have suggested possible effectiveness. These agents are not uncommonly used in clinical practice in child psychiatry, particularly in pediatric OCD patients with problematic associated anxiety. Nonetheless, placebo-controlled studies in adult OCD patients have not demonstrated benefit of these agents when added to an SSRI. Such studies are clearly warranted in pediatric OCD patients to determine their efficacy (or lack thereof) in pediatric OCD patients.

Intravenous preparations of clomipramine and other SSRIs such as citalopram have been utilized with some success in treatment-refractory adults with OCD and MDD. Similar studies are clearly warranted in treatment-refractory pediatric OCD and MDD patients.

The reader is also referred to the chapter by Grados and colleagues (1999) that provides a detailed review of advances in the pharmacotherapy of pediatric OCD.

Case History*

A 9-year-old male had undergone 3 months of intensive cognitive behavioral therapy (CBT) with no improvement in his OCD symptoms before referral to our program. He reported being plagued with “bad thoughts,” often sexual in nature, that he was “unable to clear from his mind.” Afraid that others were aware of his thoughts, he repeatedly asked his mother and teacher “Are you mad

* From Fitzgerald et al., 1999.

TABLE 4 Half-Life and Metabolic Pathways of SRIs Used in the Treatment of OCD

Drug	Half-life	Active metabolite ^a	Primary enzymatic pathway	Enzymatic inhibition
Clomipramine	32 hours	Yes	CYP2D6, CYP2C19	None
Fluoxetine	1–4 days	Yes	CYP2D6, CYP3A3/4	CYP2D6
Sertraline	24 hours	No	CYP3A3/4	CYP2D6 (mild)
Fluvoxamine	16 hours	No	CYP1A2	CYP2C19, CYP1A2
Paroxetine	24 hours	No	CYP2D6	CYP2D6
Citalopram	33 hours	No	CYP2D6	CYP2D6 (mild)

CYP = Cytochrome P.

^a Metabolite has clinically important effects (other SRIs have metabolites that may affect metabolism).

Source: Grados et al., 1999.

at me?" 10 to 20 times continuously, several times each day. At presentation, he scored 39 on the CY-BOCS, indicative of very severe illness (40 = highest score possible), and was noted to have "severe OCD" on the Clinical Global Impression (CGI) scale. He had no evidence of tics or Tourette's syndrome.

Paroxetine was begun at 10 mg/day and titrated to 40 mg/day over a month and a half with some improvement in OCD symptoms (CY-BOCS 28), but increasingly aggressive behavior and a new onset of suicidal ideation. Additional assessment revealed a complicating major depression with continued significant symptoms that, when thwarted, resulted in extreme anger and belligerence. No manic or hypomanic symptoms were noted. To target his aggressive behavior and continuing OCD, risperidone was begun at 0.25 mg twice per day and titrated over the next month to 0.5 mg every morning and 0.25 mg every evening. At the same time, his paroxetine was increased to 50 mg/day resulting in significant improvements in OCD, OCD-related aggressive outbursts and depression, with resolution of suicidal thoughts. CBT was also restarted, and in contrast to his previous experience in therapy, this time he made significant progress. Unfortunately, mild sedation and weight gain of 17 lb. were noted on the risperidone augmentation therapy. His mother reported that he was growing out of his clothes and eating more than he had ever eaten before. She wondered if this was a result of his "growing," but his 1½ inch increase in height did not fully account for the weight gain. Because of her concern about his weight, we tapered and discontinued his risperidone. Within one week of risperidone being discontinued, his OCD and aggressive behaviors had returned. Therefore, risperidone was restarted at 0.25 mg/day and titrated to 0.75 mg/day divided in three equal doses. Minimal improvement was noted over the next 2 weeks. Risperidone was then increased to 1 mg/day with a marked improvement in his symptoms over the next week that has been maintained for 7 months.

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH GROUP A BETA-HEMOLYTIC STREPTOCOCCAL INFECTIONS

Recent investigation has suggested a possible developmental subtype of OCD, tic disorders, and ADHD or their combination associated with group A beta-hemolytic streptococcal (GABHS) infections. For example, GABHS infections associated with rheumatic fever and Sydenham's chorea have been associated with increased OCD symptom exacerbations, leading to the designation of pediatric autoimmune neuropsychiatric disorders associated with GABHS as PANDAS (Swedo et al., 1998). In contrast to "nonautoimmune" OCD, which is usually characterized by a more gradual and insidious onset and course, PANDAS are associated with acute onset that can often be traced to the week, day, or even hour. Alvarenga et al. (2000) reported an increased risk for developing OCD

symptoms in patients with rheumatic fever and Sydenham's chorea. It should be noted, however, that while OCD symptoms and tics have been correlated with rheumatic fever and Sydenham's chorea in adult OCD patients, the OCD behaviors and tics remain even when there is no evidence of persistence of rheumatic fever or Sydenham's chorea, which may suggest the involvement of additional factors other than immune abnormalities alone (Thomsen and Leckman, 2000). In fact, Moshed et al. (2000) found that pediatric and adult patients with Tourette's syndrome had significantly increased antinuclear and antineuronal antibodies against rodent striatum than either OCD patients or controls. The investigators were also unable to establish a definitive association between antibody levels, clinical phenomenology, and GABHS.

Additional investigation further suggests that the PANDAS subtype of OCD and Tourette's syndrome may be considerably less common than was originally believed (Husby et al., 1976; Kiessling et al., 1993; Murphy et al., 1997; Swedo et al., 1997; McCracken, 2000). Original enthusiasm about a B-lymphocyte antigen marker, D8/17, being increased in PANDAS (Husby et al., 1976; Kiessling et al., 1993; Murphy et al., 1997; Swedo et al., 1997) has dampened as issues of its specificity for the condition remain (McCracken, 2000).

Giedd et al. (1995, 2000) have reported increased basal ganglia volumes in PANDAS patients. Peterson and colleagues (2000) confirmed this finding of increased basal ganglia volumes in PANDAS children and noted that larger basal ganglia volumes in PANDAS patients were directly correlated with increased antibody titers of antistreptolysin O and antistreptococcal DNAase B. However, this effect was most evident in PANDAS children with both OCD and ADHD.

The hypothesized association between PANDAS and GABHS has led to some clinicians using antibiotic treatment (e.g., penicillin) to treat OCD and tic symptom exacerbations. Garvey et al. (1999) conducted an 8-month penicillin vs. placebo crossover study comparing the efficacy of oral penicillin vs. placebo prophylaxis in preventing GABHS infections, thereby reducing OCD symptoms. No significant differences were observed in the penicillin or placebo arms of the study, although the investigators speculated that higher doses of penicillin may have been necessary. Clinicians are continuing to prescribe antibiotics both acutely and chronically to help pediatric patients with OCD and tic disorders whose illness appears to be associated with GABHS infections. However, many questions remain, including: (1) How long should a child be treated with an antibiotic? (2) What is the optimal dosage to use? (3) Will resistance and/or side effects develop? and (4) Which antibiotic for which child? Because of these outstanding questions, *we do not recommend* routine antibiotic prophylaxis or use in children with OCD and/or tic disorders associated with streptococcal infections. In the case of documented GABHS infections and together with the child's pediatrician or family practitioner, treatment of the acute illness in standard fashion is appropriate. This would be similar to treating any child diagnosed with a

GABHS infection with or without associated neuropsychiatric symptoms. Given concerns about antibiotic resistance, overprescription for nonbacterial/viral etiologies, routine use of antibiotics in this population cannot be endorsed pending further investigation.

Plasma exchange and intravenous immunoglobulin (IV IgG) therapy has been used in severely ill, treatment-refractory pediatric patients with OCD and tic disorders (Allen et al., 1995; Perlmutter et al., 1999). Perlmutter et al. (1999) conducted a randomized controlled study in which 30 children with severe OCD and tic disorders were randomized to plasma exchange, IV IgG, or placebo. Twenty-nine children finished the trial. Both plasma exchange and IV IgG significantly decreased OCD and tic symptom severity. Follow-up penicillin prophylaxis for at least 2 years also demonstrated possible efficacy.

Plasmapheresis has also been associated with a decrease in enlarged basal ganglia volumes in PANDAs patients (Giedd et al., 1996). This contrasts with findings in non-PANDAS OCD patients where decreased basal ganglia volumes have been reported (Luxenberg et al., 1988; Rosenberg et al., 1997) and illustrates how neurobiological studies delineating specific subtypes of illness may have critical relevance for treatment development. Translation of such advances in developmental neuroscience into clinical assessment and treatment trials in OCD will likely result in better treatment for this heterogeneous condition.

Neither plasmapheresis nor IV IgG can be recommended as standard therapy for any patients with OCD or tic disorders. Standard pharmacological treatment (as described in this chapter) and cognitive behavioral/psychotherapeutic approaches are clearly warranted. More invasive approaches such as plasmapheresis and IV IgG are considered experimental and should be considered only after standard treatment options have proven to be ineffective. To our knowledge, Dr. Swedo's group at the National Institute of Mental Health (NIMH) is the only group currently offering plasmapheresis or IV IgG for eligible PANDAS patients with OCD and tic disorders. Lorraine Lougee is the contact person at NIMH for clinicians who wish to determine whether or not a patient they are seeing may be eligible for this treatment (phone 301-496-5323).

Tourette's Disorder

The SSRIs are not generally considered to be effective for primary tic disorders such as Tourette's syndrome (Grados et al., 1999). However, tic disorders and Tourette's syndrome are frequently associated with OCD behaviors and frank OCD (Zohar 1999; Pollock and Carter, 1999). In such cases, SSRIs have been used.

Open-label studies using SSRIs to suppress tics and OCD symptoms in patients with Tourette's syndrome have demonstrated reduction in motor and vocal tics in some reports, although contrary reports exist (Riddle et al., 1990a;

Como and Kurlan, 1991; Buckingham and Gaffney, 1993). Kurlan et al. (1993) conducted a controlled study comparing fluoxetine to placebo in treating 11 children with Tourette's syndrome and OCD and noted a relatively modest effect of fluoxetine on OCD symptoms in these patients. Fluoxetine showed no benefit in reducing tic symptoms. Scahill et al. (1996) conducted a double-blind, placebo-controlled study in 14 patients with Tourette's syndrome and OCD and found that fluoxetine had no significant impact on tic symptoms. While a mean reduction of 37.5% in OCD symptom severity was observed in these patients, this did not differ significantly from placebo. Both studies had a small sample size, so larger studies are clearly warranted to determine the efficacy of SSRIs in obsessive-compulsive behaviors/disorder and comorbid tic disorders. It should be noted that recent investigation has suggested that behavior modification therapy can reduce certain tic behaviors in patients with chronic tic disorders including Tourette's syndrome (Shaffer et al., 1996). Therefore, cognitive behavioral therapy should be considered in OCD patients with and without comorbid tic disorders.

Selective Mutism

Recent investigation has suggested that the SSRIs may be effective in treating selective mutism. Black and Uhde (1992a) have speculated that selective mutism may actually represent a variant of social anxiety disorder (social phobia) and reported a case that responded well to fluoxetine treatment. Motavalli (1995) also reported that fluoxetine was effective in treating a case of selective mutism. In a double-blind, placebo-controlled study comparing fluoxetine to placebo in six patients with selective mutism, Black and colleagues (1992b) found that four of the six patients responded to fluoxetine treatment after 12 weeks of therapy. Dummit et al. (1996) treated children 5–14 years of age with selective mutism with a 9-week open-label trial of fluoxetine 10–60 mg/day and noted that 76% of children experienced reduced anxiety, increased speech, and overall global improvement in their condition.

The other SSRIs (paroxetine, fluvoxamine, sertraline, and citalopram) should also be investigated to determine their potential role in the treatment of selective mutism. With their favorable side-effect profiles, they may have utility for this condition. Medication treatment may also facilitate cognitive behavioral psychotherapy as children's speech increases, anxiety decreases, and their condition improves. Controlled studies are clearly warranted.

Attention-Deficit Hyperactivity Disorder

Attention-deficit hyperactivity disorder (ADHD) has most often been conceptualized as a disorder of catecholamine underactivity with dysregulation in dopaminergic and noradrenergic systems. Serotonergic systems have not typically been implicated in the pathogenesis of ADHD. Treatment of ADHD with the serotonin

agonist fenfluramine has not been found to be efficacious (Donnelly et al., 1989). In recent years, however, renewed investigation searching for new psychopharmacologic treatments for ADHD has been spurred in view of the psychostimulants being classified by the FDA as Schedule II, the most restrictive classification for drugs considered to be medically useful (Physicians' Desk Reference, 2001) and the potentially problematic side-effect profile associated with the TCAs (particularly potential cardiac side effects). This has led to the SSRIs being revisited in the psychopharmacological treatment of ADHD.

Barrickman and colleagues (1991) used fluoxetine to treat 19 children and adolescents with ADHD. It was administered in open-label fashion for 6 weeks, and nearly 60% of the patients were rated as being at least moderately improved. All patients received between 20 and 60 mg of fluoxetine per day. Adverse effects were noted to be minimal, and most of them resolved spontaneously or with dosage adjustment. Interestingly, almost all of the subjects responded within one week after achieving the therapeutic dose. Gammon and Brown (1993) found that open-label fluoxetine-methylphenidate combination therapy was effective in treating ADHD and comorbid MDD.

This finding is important because although other antidepressants (such as desipramine, imipramine, and bupropion) have been found to be effective in the treatment of ADHD, some patients respond only partially, or not at all, to stimulants, TCAs, and bupropion. This underscores the need for additional medication options, since up to 30% of patients treated with stimulants fail to respond (see Chapter 7). Fluoxetine has the additional advantage of once-a-day dosing, thus avoiding the need to take the medication during school hours. Moreover, its long half-life may be beneficial in that, not uncommonly, teachers observe more improvement in children on stimulants than do parents, because their effects have often worn off by the time the child returns home from school. Because of fluoxetine's long half-life, its efficacy may continue while the child is at home. Double-blind, placebo-controlled studies are necessary to evaluate whether the SSRIs have any role in the treatment of ADHD.

There are no published reports investigating the efficacy and safety of the other SSRIs (paroxetine, fluvoxamine, sertraline, or citalopram) in the treatment of ADHD. With their favorable side-effect profile, they may have utility for this condition. There have been no double-blind, placebo-controlled studies of the SSRIs in ADHD. Such studies are clearly warranted to determine whether or not the SSRIs may have a role in the treatment of ADHD with and without comorbid conditions (see also Chapter 7).

Anxiety/Panic Disorders

Birmaher and colleagues (1994) found that open-label fluoxetine treatment was effective in treating children with non-OCD anxiety disorders. A recent 8-week

double-blind, placebo-controlled study of 128 children with anxiety disorders including generalized anxiety disorder, separation anxiety disorder, and social phobia comparing fluvoxamine and placebo found fluvoxamine to be superior to placebo (Research Units of Pediatric Psychopharmacology (RUPP) Anxiety Group, 2001). Seventy-nine percent of patients responded to fluvoxamine therapy, whereas less than 30% of patients responded to placebo. Doses were initiated at 25 mg/day and were increased in a flexible dosage design up to a maximum daily dose of 250 mg/day in children 6–12 years of age and 300 mg/day for adolescents 13–17 years of age (mean daily dosage 100 mg). The improvement noted with fluvoxamine in this study exceeded improvement reported in studies of anxious adults treated with TCAs and benzodiazepines. Dr. Riddle, a co-investigator on this study, however, commented that these results are not likely to result in FDA approval of fluvoxamine for pediatric anxiety, pointing out that the FDA requires that a medication be studied for one disorder as opposed to the three anxiety disorders studied in this investigation (Borzo, 2000). SSRIs are, however, becoming first-line treatment for non-OCD pediatric anxiety disorders. Many clinicians will prescribe benzodiazepines during the initial titration phase of SSRIs in pediatric anxiety disorders since SSRI efficacy may be delayed. We advise careful screening for personal history of substance abuse and family history of substance abuse when benzodiazepines are prescribed with SSRIs. We also advocate that the prescribing clinician explain to the parents and child that the anticipated role of the benzodiazepine is short term and that efforts to taper and discontinue the benzodiazepine will be made once SSRI treatment efficacy has been established. Long-term fluvoxamine treatment of pediatric non-OCD anxiety may also be effective (Walkup, 2000).

Rynn et al. (2001) recently conducted a double-blind, placebo-controlled study evaluating the safety and efficacy of sertraline in the treatment of 22 children and adolescents 5–17 years of age with generalized anxiety disorder. Sertraline was started at 25 mg/day for the first week and increased to 50 mg/day for weeks 2–9 of the study. Sertraline treatment was significantly more effective than placebo in the treatment of children adolescents with generalized anxiety disorder. Differences in treatment in favor of sertraline were first evident at week 4 of treatment. These results suggest that sertraline treatment at doses of only 50 mg/day was effective and safe in the treatment of pediatric generalized anxiety disorder. In adults with anxiety disorders, antidepressant treatment may be more effective in reducing psychic than somatic symptoms of anxiety (Rickels et al., 2000; 1993). However, Rynn et al. (2001) observed that sertraline was effective in reducing psychic and somatic anxiety symptoms.

There are no data on the use of paroxetine, or citalopram in pediatric anxiety disorders. While fluoxetine, paroxetine, sertraline and citalopram have been demonstrated to be effective in the treatment of panic disorder in adults, there are no controlled data in children and adolescents. Renaud et al (1999) treated

nine pediatric patients with panic disorder with fluoxetine (mean dose 34.4 mg/day, range 20–60 mg/day), 2 pediatric panic disorder patients with paroxetine 20mg/day and one panic disorder patient with sertraline 125 mg/day and found this open label treatment to be well tolerated and effective. Paroxetine has also recently been FDA-approved to treat social anxiety disorder (social phobia) in adults. A multicenter double-blind placebo-controlled trial of paroxetine for social anxiety disorder in children and adolescents is underway. These areas merit further study, since TCAs have not consistently been shown to be superior to placebo in pediatric anxiety disorders (See Chapter 8). Moreover, the SSRIs, in contrast to the benzodiazepines, are not addictive.

Premenstrual Dysphoric Disorder

Fluoxetine has recently been FDA-approved for treating premenstrual dysphoric disorder (PMDD). Because of Eli Lilly's concerns that there may be stigma associated with the brand name prozac, they are marketing fluoxetine as Sarafem. Sarafem and prozac are identical except for having different colored capsules (Mechcatie 2000b). Fluoxetine has been found to be safe and effective in the treatment of PMDD in seven randomized, double-blind, placebo-controlled studies (Muller, 1999). In the largest study conducted by Steiner and colleagues (1995), fluoxetine reduced both the emotional and physical symptoms associated with PMDD. Two smaller randomized double-blind, placebo-controlled studies (Pearlstein et al., 1997; Su et al., 1997) confirmed the efficacy and safety of fluoxetine in PMDD. Pearlstein and colleagues' (1997) study was distinguished by its comparing the effectiveness of fluoxetine vs. placebo and bupropion. Two separate comparisons were conducted over 2–6 months in this study: (1) fluoxetine 20–60 mg/day was compared with placebo and (2) fluoxetine 20 mg/day was compared with bupropion 300 mg/day and placebo. Significantly greater improvement in mood and physical symptoms and significantly decreased functional impairment were observed in women treated with fluoxetine. Fluoxetine doses of 60 mg/day tended to be somewhat more effective than doses of 20 mg/day, although this was not statistically significant. Improvement in mood and physical symptoms and decreased functional impairment were frequently noted in the first menstrual cycle of women treated with fluoxetine.

A 2-month randomized crossover double-blind, placebo-controlled study comparing sertraline and placebo found sertraline to be superior to placebo in alleviating PMDD symptoms (Jermain et al., 1999). PMDD patients were treated with sertraline or placebo for 2 months each during the luteal phase. Treatment was started 2 weeks before onset of menstrual period and stopped the day the menstrual period started. Sertraline 50 mg/day was used during the first luteal phase and was increased to 100 mg/day in patients who failed to achieve a 30% reduction in PMDD symptoms. There are no data on the use of SSRIs in adoles-

cents with PMDD. Given their efficacy in adults, controlled study is warranted in adolescents.

Self-Injurious Behavior

King (1991) reported a single case in which fluoxetine, 40 mg/day, reduced self-injurious behavior (SIB), including head banging and biting, in a 19-year-old with moderate mental retardation. This reduction in SIB lasted about 60–70 days. The consensus of the treatment team was that the incidence of SIB then returned to that of prefluoxetine treatment.

On the other hand, Bass and Beltis (1991) observed a significant and sustained reduction in SIB in a 17-year-old male with severe to profound mental retardation who was treated openly with fluoxetine. They reported a 40–50% reduction in SIB accompanied by improvement in mood lability, motor capacities, and social activity. No adverse effects or decreased therapeutic effects were observed during 2 years of treatment at daily doses of 40 mg. Twelve weeks before being started on fluoxetine, the patient had been unresponsive to naltrexone, an opiate receptor blocker, in a double-blind, placebo-controlled trial.

Velazquez and Ward-Chene (2000) reported that open-label fluoxetine treatment was effective in reducing self-mutilating behavior in an 11-year-old boy. This was a rather dramatic case in which the boy had begun mutilating himself during early childhood, chewing his right hand third, fourth, and fifth fingers to the second phalanges. The patient also was diagnosed with comorbid dysthymia and impulse control disorder not otherwise specified. He did not meet criteria for OCD as measured by the Yale-Brown-Obsessive Compulsive Scale. After 1 month of treatment with fluoxetine 20 mg/day, the 11-year-old boy stopped chewing his fingers. His dysthymic symptoms also decreased and his aggression decreased dramatically. He did well for 5 months but then failed to follow up with treatment and began self-mutilating and chewing his fingers while off the fluoxetine. At age 15 years, he returned to treatment, chewing his fingers to a lesser extent. However, he could not stop himself from doing this even though he understood that by chewing he would make his fingers smaller. He was restarted on fluoxetine 20 mg/day, and his symptoms and chewing behavior resolved after 2 months of therapy. The authors reported that after 3-year follow-up, the patient's self-mutilating behaviors, chewing, and other impulse dyscontrol are markedly improved when he is taking the fluoxetine.

These studies support the hypothesis that SIB may have an obsessional and compulsive quality, and thus may be expected to respond to alterations in the serotonin system. This is further supported by previous reports of the partial efficacy of the treatment of SIB in children with Lesch-Nyhan syndrome with serotonin precursor L-5-hydroxytryptophan (Anders et al., 1978; Custells et al., 1979).

Open-label pharmacotherapy with SSRIs including fluoxetine, fluvoxamine, and sertraline have been reported to be effective in decreasing repetitive thoughts and behaviors, anxiety, self-injurious behaviors, and depressed mood in children with pervasive developmental disorders (Scahill and Koenig, 1999). An open trial of fluoxetine, in doses ranging from 20 to 80 mg/day, resulted in a significant improvement in Clinical Global Impressions ratings of clinical severity in 15 of 23 patients with DSM-III-R diagnoses of autistic disorder and in 10 of 16 patients with mental retardation (Handen et al., 1991). It should be noted, however, that 6 of the 23 patients with autistic disorder and 3 of the 16 patients with mental retardation experienced side effects that significantly interfered with functioning. These consisted primarily of restlessness, hyperactivity, agitation, decreased appetite, or insomnia. Mentally retarded patients (and perhaps autistic patients, as well) may be more susceptible to the side effects of psychotropic medications and have, in fact, been found to be more susceptible to methylphenidate-induced side effects (Handen 1991; Aman et al., 1991). Lower doses of SSRIs may be warranted, with very gradual increments (see Dosing and Administration). This area deserves more investigation, and placebo-controlled studies are urgently needed. Future study should utilize double-blind, placebo-controlled trials and stringent behavioral measures. As it can be difficult to diagnose psychopathology in children with autism and mental retardation, therapy is difficult, and the accurate quantification of therapeutic effect can be enormously challenging. Nonetheless, this population has tremendous needs meriting additional controlled investigation.

Drug Craving

See Chapter 19.

Trichotillomania

The serotonergic agent clomipramine has been found to be effective in the treatment of trichotillomania (a disorder believed to have an obsessive-compulsive component) and in the treatment of autistic children with disturbances in social relatedness, obsessive-compulsive symptoms, impulse control problems, and/or aggressive behaviors (McDougle et al., 1992) (see Indications in Chapter 8). A recent review of the use of serotonin reuptake inhibitors in trichotillomania casts doubt on the efficacy of these medications in trichotillomania (Jaspers, 1996). Double-blind, placebo-controlled studies are needed to determine whether or not SSRIs have a role in treating trichotillomania.

Anorexia Nervosa

Fluoxetine has been shown to be effective in reducing relapse in adult patients with anorexia nervosa in the weight-recovered state. It has not been found to be

effective in treating anorexia nervosa patients in the weight-depleted state. However, there are no data on children and adolescents. This area merits further study since TCAs, clomipramine, and other psychotropic agents such as lithium, diazepam, metoclopramide, sulpiride, cyproheptadine, and pimozone, have failed to produce significant improvement (Goldberg et al., 1979; Lacey and Crisp, 1980; Gross et al., 1981; Halmi et al., 1982; Vandereycken and Pierloot, 1982; Vandereycken, 1984; Biederman et al., 1985; Crisp et al., 1987). There is, however, recent enthusiasm for investigating the role of atypical neuroleptics (e.g., risperidone, olanzapine) that have potentially significant weight gain side effects in treating patients with anorexia nervosa (see Chapter 12).

When SSRIs are used in patients with anorexia nervosa, we advise caution as these medications have been associated with weight loss. Placebo-controlled study is necessary. If they are employed, close monitoring is essential.

Bulimia Nervosa

The SSRIs may be ideal agents for this disorder (Wermuth et al., 1977; Pope et al., 1983; Mitchell and Groat, 1984; Walsh et al., 1984; Kennedy et al., 1985; Hughes et al., 1986; Kennedy et al., 1986). The cycle of bingeing and purging in bulimia has often been characterized as having a compulsive and/or obsessive quality, for which the SSRIs may be especially effective. Comorbid mood disorders are also quite prominent in patients with bulimia nervosa. In addition, bulimic patients are notoriously prone to impulsive acts, such as suicide attempts. The SSRIs are less lethal in overdose than are the TCAs (see Overdose).

Fluoxetine is now FDA-approved for treating adult patients with bulimia nervosa. Foss and associates (1990) conducted a double-blind, placebo-controlled study of 6 weeks duration, with a double-blind extension period of 18 weeks, of patients judged to be treatment responders. Fluoxetine or placebo was randomly administered to 40 women with bulimia nervosa. All received placebo on a single-blind basis during the second week of the study. The investigators defined success as the patient's no longer meeting the DSM-III-R criteria for bulimia nervosa or the frequency of bingeing and purging decreasing to less than 50%. In the fluoxetine group, 18 patients completed the initial 6-week study and 16 the entire study. In the placebo group, however, 18 completed 6 weeks, and then 15 withdrew because of lack of therapeutic effect. Two patients stopped after 12 weeks, and only one patient was able to complete the entire 24 weeks. Foss and associates concluded that fluoxetine at 60 mg/day was significantly more effective in the treatment of bulimia than was placebo.

Fava and colleagues (1990) studied the long-term effectiveness of fluoxetine in the treatment of 19 outpatients with bulimia nervosa who had been treated with fluoxetine for more than 3 months. Retrospective analysis was conducted to gather data regarding three distinct periods in the course of the illness: (1) be-

fore treatment, i.e., patient baseline; (2) 6–8 weeks into treatment; and (3) at the end of treatment, i.e., on discontinuation, or at the time of data collection if the patient was still on fluoxetine. At follow-up, 13 of 19 patients were on fluoxetine, whereas 6 patients had discontinued. The frequency of binges per week significantly decreased during fluoxetine treatment in all patients. The authors concluded that fluoxetine was shown to have produced a significant improvement in binge-and-purge frequency at follow-up.

Walsh and colleagues (2000) conducted an 8-week double-blind, placebo-controlled study comparing fluoxetine and placebo in 22 patients with bulimia nervosa who had proven refractory to or relapsed after being treated with cognitive behavioral therapy or interpersonal psychotherapy. Nine patients were randomized to receive placebo, and 13 patients were randomized to fluoxetine 60 mg/day. Binge eating decreased from 22 to 4 episodes in patients treated with fluoxetine, while binge eating increased from 15 to 18 episodes in patients treated with placebo. Purging frequency decreased from 30 to 6 episodes in patients treated with fluoxetine, while purging frequency actually more than doubled (15 to 38 episodes) in patients treated with placebo.

It is important to note that the short-term efficacy of SSRIs has not been shown to be greater than that reported for TCAs and MAOIs (Herzog, 1992). The chief advantage of the SSRIs lies in their relative safety as compared with these other medications. Nonetheless, patients who improve on any of these drugs often have persistent bulimic symptoms. Additional study is necessary to determine the long-term effectiveness of SSRIs in the treatment of bulimia. Bulimics frequently exhibit significant shifts in their body weight. There are no data in children and adolescents underscoring the need for double-blind, placebo-controlled investigation in this population.

Prader-Willi Syndrome

The Prader-Willi syndrome (PWS) is a congenital disorder characterized by obesity, small stature, hypogonadism, hyperphagia, and mental retardation, and it occurs in one in 10,000–15,000 live births (Prader et al., 1956; Cassidy 1987a, 1987b). Psychiatric complications are common, including aggression, behavioral disturbances, and depression. The patient's hoarding of and preoccupation with food often takes on an obsessional and ritualistic character, and desperate parents may be forced to padlock their refrigerators and keep all food out of reach of these children. Behavioral and psychotherapeutic interventions have been largely unsuccessful, as have pharmacological approaches, including neuroleptics, standard antidepressants, lithium, carbamazepine, and methylphenidate. These agents have the added disadvantage (except for methylphenidate) of either causing weight gain or increasing appetite craving. The initial excitement regarding a role for opiate receptors in the pathology of the illness and the potential utility

of naloxone and naltrexone has largely dissipated as these agents have been shown to be ineffective.

Recent excitement has been generated, however, regarding the SSRIs. These agents may be less likely to cause weight gain and may suppress appetite. In addition, they are effective in the treatment of OCD. Since the hoarding and overeating behavior exhibited by PWS patients has often been described as obsessional in nature, these medications may be useful in these patients as well. Of depressed patients being treated with fluoxetine, 13% experienced some weight loss. Dech and Budow (1991) described a 17-year-old female with PWS, including mild mental retardation, compulsive eating with gross obesity, and trichotillomania and trichophagia. The patient had a long history of multiple cognitive, behavioral, and pharmacological treatments, including several inpatient hospitalizations that had met with only limited success. She demonstrated a marked improvement in weight control and a moderate improvement in hair pulling over a 6-month period of observation at a dose of 80 mg/day.

Selikowitz and associates (1990) provided further evidence of a possible role for serotonergic agents in the treatment of this disorder. They conducted a double-blind, placebo-controlled trial to determine the effect of fenfluramine on the weight and behavior of patients with PWS. Fenfluramine treatment was associated with significant weight loss, an improvement in food-related behavior, and a decrease in aggressive behavior directed toward others. Skin picking and other self-mutilation were, however, unaffected. None of the patients suffered any side effects while on the medication. Thus, the SSRIs may have an important role in the treatment of some patients with PWS. Further study is clearly warranted.

Borderline Personality Disorder

SSRIs are not uncommonly prescribed in treating adult patients with borderline personality disorder. These patients often exhibit impulsivity, aggression, and may make suicidal gestures, such as cutting themselves, and exhibit prominent shifts in mood. As CNS serotonin deficiency has been associated with impulsivity, aggression, and severity of suicide attempts, and with suicide completions as evidenced in postmortem brains, these agents may be helpful in treating this condition. Moreover, because of their relative safety when taken in overdose and their benign side-effect profile, their risk-benefit ratio is favorable. In addition, patients with borderline personality disorder often have comorbid mood disorders for which these agents may be helpful.

Posttraumatic Stress Disorder

Sertraline is currently the only FDA-approved pharmacological treatment for adults with posttraumatic stress disorder (PTSD). Recent investigation has also found fluoxetine to be superior to placebo in treating adults with PTSD (Malik

et al., 1999). Improvement was noted in 41% of patients treated with fluoxetine but only 4% of patients treated with placebo. Moreover, chronic treatment for at least 6 months with fluoxetine resulted in significant additional improvement in PTSD patients (Davidson, 2000). Current recommendations are to maintain effective SSRI treatment in PTSD patients for 1 year or longer (Ballenger et al., 2000). However, it is not clear whether this improvement in patients with PTSD represents a specific effect on the PTSD condition or is a secondary result due to improvement in depression.

SSRIs are relatively safe medications for the treatment of patients with PTSD. A recent open label trial of citalopram in adolescents with PTSSD (Seedat et al., 2001) reported improvement in PTSD symptoms. There are no controlled data on children and adolescents, and further controlled study is warranted.

CONTRAINDICATIONS

See Table 5.

History of Allergic Reaction

A known hypersensitivity to SSRIs is an absolute contraindication to their use. It should be noted, however, that sometimes the allergic reaction is to the dye in the tablet capsule and not the SSRI itself.

Patients on MAOIs

SSRIs should not be prescribed to any patient who has received an MAOI within 2 weeks (5–6 weeks for fluoxetine). Conversely, an MAOI should not be started within 5 weeks of using an SSRI (see Chapter 11). In patients receiving both an SSRI and an MAOI, there have been reports of severe, sometimes fatal, reactions. Some cases had features resembling those of the neuroleptic malignant syndrome.

Patients on Hypericum (St. John's Wort)

SSRIs should not be prescribed to patients currently taking hypericum (St. John's wort) because of risk of serotonin syndrome (see Chapter 17). It is important

TABLE 5 Contraindications to Using SSRIs

Known hypersensitivity reaction
On MAOI within past 5 weeks (fluoxetine) or past 2 weeks (other SSRI)
Currently on hypericum (St. John's wort)
Pregnancy
Liver disease

to screen patients and their parents about over-the-counter herbal medications, including St. John's wort, when prescribing SSRI medications.

Pregnancy

Large uncontrolled studies suggest that the SSRIs are safe during pregnancy. Recent investigation of 969 Swedish women from the Swedish Medical Birth Registry (including information from prenatal care visits, delivery to the first pediatric examination of the child) who used antidepressants during pregnancy found the incidence of birth defects (4%) and infant mortality (0.7%) to be no different from rates of birth defects and infant mortality in the general population (Ericson et al., 1999). The investigators reported increased smoking, parity, and age in women taking antidepressants during pregnancy than women in the general population. Women taking SSRIs showed a trend for delivering infants preterm (less than 37 weeks of gestation) and with lower birth weight. In contrast, pregnant women taking non-SSRI antidepressants were found to have somewhat heavier infants than the general population. However, low birth weight in children of pregnant women who took SSRIs during pregnancy did not remain significant after controlling for age, parity, and smoking. Five hundred and thirty-one women used SSRIs only during pregnancy, 15 were treated with combination of an SSRI and other antidepressant, and 423 were treated with a non-SSRI antidepressant (Ericson et al., 1999).

Citalopram was prescribed to 39% of the women in this sample. There had been no previous data on citalopram and potential teratogenic effects. Birth defects and infant mortality were comparable to those observed in infants whose mothers had taken other SSRIs during their pregnancy. Fluoxetine, paroxetine, and sertraline were also SSRIs taken by pregnant women in these data from the Swedish Medical Birth Registry.

It should be noted that obstetricians are not uncommonly treating pregnant women with SSRIs, particularly fluoxetine, for which available data do not suggest increased risk for birth defects or infant mortality. Conversely, many clinicians including psychiatrists, primary care givers, etc., administer strong warnings about getting pregnant while on SSRI or other psychotropic medications and advocate discontinuation of medication during pregnancy and if the woman decides to breast feed. Dr. Zachary Stowe, Director of the Pregnancy and Postpartum Mood Disorders Program at Emory University in Atlanta, Georgia, conducted a multicenter prospective study of 112 women being treated with antidepressants who became pregnant and then discontinued antidepressant medication when discovery of pregnancy was made (Lindsay, 2000). Approximately 70% of these women developed significant depressive symptoms during their pregnancy, and 50% were restarted on their antidepressant. It was also pointed out that not infrequently, women do not find out they are pregnant until the fourth

or fifth week, so that organogenesis has already been initiated (Lindsay, 2000). Dr. Stowe also studied 90 women being treated with the SSRIs, fluoxetine, paroxetine, or sertraline during pregnancy. The SSRIs cross the placenta incompletely, and in this study all babies were born in good health, with normal height and weight, with complication rates that were actually lower than those seen in the general population (Lindsay, 2000). Thus, many now advocate the use of SSRIs and other medications in cases of life-threatening psychiatric processes as the risk to the fetus and unborn baby may be greater in a mother under considerable psychiatric distress.

There are no data in pregnant children and adolescents treated with SSRIs. Multicenter studies of SSRIs in children and adolescents sponsored by industry and the NIH have typically excluded pregnant girls from study. This is done in part because the efficacy and safety of SSRIs has not been established in pediatric populations. Many of these studies are also measuring pharmacokinetics in children and adolescents, and these measures may be different in pregnant girls. It is also not known whether there may be teratogenic effects of SSRIs at specific periods of developmental maturation. We recommend use of these medications in pregnant teenagers only with life-threatening psychiatric processes that pose grave danger to the mother and fetus. In such cases it is critical to work closely with an obstetrician and discuss the risks/benefits with the pregnant teenager and her parents and family. Such cases would be considered high risk and merit high-risk monitoring.

Liver Disease

These medications should be given cautiously in patients with liver disease as the elimination half-life of fluoxetine and other SSRIs can be prolonged. In patients with cirrhosis, half-lives of fluoxetine were increased to 7.6 days as compared to the normal range of 2–3 days (Physicians' Desk Reference, 2001). Interestingly, 12 patients with MDD on dialysis who were treated with fluoxetine 20 mg/day were found to have comparable steady-state fluoxetine and norfluoxetine concentrations to those observed in patients with normal renal function (Physicians' Desk Reference, 2001). Nonetheless, caution is still warranted when prescribing SSRIs to patients with abnormal renal function.

SIDE EFFECTS

The reader is also referred to an excellent recent article detailing SSRI side effects in children and adolescents (Walkup et al., 2001) (see Table 6).

Gastrointestinal Complaints

Gastrointestinal complaints, including nausea, diarrhea, and dyspepsia, are very common side effects in patients treated with SSRIs. Nausea was observed in 33%

TABLE 6 Side Effects of SSRIs

Common:

- GI (nausea, diarrhea, dyspepsia)
- Decreased appetite
- Weight loss
- Nervousness
- Insomnia
- Excess sweating
- Sedation
- Dream intensification
- Motor restlessness/abnormal motor movements
- Dry mouth
- Male sexual dysfunction, anorgasmia

Occasional:

- Social disinhibition
- Subjective sensation of excitation
- Hypomania/mania
- Rash/allergic reactions
- Seizure
- Hair loss

Side effects of heterocyclic agents not seen:

- Anticholinergic
- Cardiovascular

There is no evidence that self-destructive phenomena (i.e., suicidal ideation/attempts) are more common with fluoxetine than with other antidepressants.

of 15 adolescents treated with fluoxetine (Boulos et al., 1992). Gastrointestinal distress was also reported in 15% of 20 children and adolescents treated with paroxetine. Tolerance to nausea often develops after 1–2 weeks on the drug (Cole and Bodkin, 1990). Donnelly et al. reported the results of two ten week multicenter, double-blind, placebo-controlled studies of sertraline in the treatment of 376 outpatients with MDD 6–17 years of age at the 2001 annual meeting of the American College of Neuropsychopharmacology December 12, 2001. Diarrhea and vomiting were observed in greater than 5% of patients treated with sertraline and more than two times as many patients treated with placebo.

A recent epidemiological investigation evaluated the link between SSRIs and upper gastrointestinal bleeding (de Abajo et al., 1999). The investigators studied 1651 cases of upper GI bleeding and 248 cases of ulcer perforation and reported that the risk for upper gastrointestinal bleeding was three times greater in patients being treated with SSRIs. Subjects were being treated in general practice in England and were compared to 10,000 controls matched for age, sex, and year of identification of the case. Current SSRI treatment was found in 52 of

1651 patients (3.1%) with upper gastrointestinal bleeding as opposed to 95 of 10,000 controls (1%). Controlling for sex, age, SSRI dose, or duration of treatment with the SSRI did not dilute or alter this effect. De Abajo and colleagues (1999) found no association between non-serotonergic antidepressants and upper gastrointestinal bleeding. Combination of SSRIs and nonsteroidal anti-inflammatory agents also increased the risk of upper gastrointestinal bleeding likely by SSRI mediated increases in nonsteroidal anti-inflammatory concentrations.

The authors (de Abajo et al., 1999) noted that SSRI-induced serotonin release from platelets in the gastrointestinal system may be involved since release of serotonin from platelets is critically involved in the regulation of hemostatic responses in injury to blood vessels. There are limited data in children and adolescents. Lake and colleagues (2000) found increased bruising or epistaxis in five children and adolescents 8–15 years of age 1–3 months after starting treatment with an SSRI. However, close monitoring and study is indicated, particularly since prescriptions of SSRIs have increased markedly in pediatric populations. Moreover, nonsteroidal anti-inflammatory agents are not uncommonly used in pediatric populations.

Weight Loss

Weight loss and decreased appetite are reported side effects with fluoxetine. Actual weight loss may be less common with the other SSRIs, sertraline, paroxetine, fluvoxamine, and citalopram. A weight loss greater than 5% of body weight was seen in 13% of patients treated with fluoxetine, as compared with 4% of patients treated with placebo and 3% of patients treated with TCAs (Physicians' Desk Reference, 2001). Nine percent of patients experienced anorexia, but patients rarely discontinue the treatment because of weight loss. Boulos and colleagues (1992) noted that 5 of 15 (33%) adolescents on fluoxetine had anorexia. It should be pointed out, however, that weight gain associated with TCAs is frequently a distressing side effect, although some investigators have argued that weight gain can also be seen in some patients treated with SSRIs.

More recent longer-term investigation, in fact, casts some doubt on long-term weight changes induced by SSRIs. Michelson and colleagues (1999) conducted a randomized, placebo-controlled trial in which adult MDD patients whose symptoms had remitted after 12 weeks of treatment with fluoxetine were randomly assigned to 38 weeks of fluoxetine or placebo. Weight was assessed regularly during the 12-week acute treatment trial and after 14, 26, and 38 weeks during chronic therapy. The investigators also analyzed the association between body mass index (BMI) and weight and appetite change. During the first 4 weeks of open-label fluoxetine treatment, a mean decrease in weight of 0.4 kg was noted. However, the mean absolute increase in weight was comparable in patients who completed 50 weeks of therapy with either fluoxetine or placebo. Interestingly, weight increase was most related to pretreatment poor appetite and improved

appetite after remission of their depression and none of the patients stopped treatment because of weight gain. Thus, acute fluoxetine therapy appears to be associated with a moderate reduction in weight in MDD patients. After recovery from MDD, weight gain is comparable in patients taking fluoxetine and placebo and likely reflects improvement in depression. Decreased or problematic appetite is a characteristic symptom of MDD. Further study is clearly warranted, particularly in child and adolescent populations where physical growth is occurring.

Nervousness and Insomnia

Nervousness and insomnia are very common side effects of SSRIs. Unpublished data on 117 patients at McLean Hospital treated with fluoxetine show that patients with these symptoms before fluoxetine therapy do slightly better than those without these symptoms at baseline (Cole and Bodkin, 1990). Changing the time of drug administration often fails to affect the insomnia. Riddle and colleagues (1990b) found that sleep disturbances occurred in 11 of 24 patients treated with fluoxetine, 20–40 mg/day, for depressive or obsessive-compulsive symptoms. Of 15 adolescents treated with fluoxetine, 20% reported feeling tense and 13% had difficulty sleeping while receiving the medication (Boulos et al., 1992). Rosenberg and colleagues (1999) also observed insomnia in 15% of 20 pediatric OCD patients treated with paroxetine 10–60 mg/day.

In adults, trazodone, 25–50 mg at bedtime, has proved helpful for SSRI-induced insomnia (Arana and Hyman, 1991). It should be noted, however, that some patients receiving trazodone and SSRIs exhibit cognitive impairment. Caution is also indicated as the combination may increase the risk for sick serotonergic syndrome. There are no data on the use of trazodone-SSRI combinations for children and adolescents. In general, monodrug therapy is preferable although polydrug therapy is sometimes necessary. In a patient whose depressive or OCD symptoms appear to be responding to SSRI treatment, but who continues to have problems with insomnia, the cautious addition of low-dose trazodone may be helpful. In contrast to the benzodiazepines, trazodone is sedating without being addictive. In a patient suffering from insomnia, the clinician should be alert for possibly evolving hypomania/mania, particularly if other manic-like symptoms become evident. A thorough medical work-up to look for associated primary sleep disturbances is also indicated.

Excess Sweating

One third of all patients treated with fluoxetine by Boulos et al. (1992) had increased sweating, a relatively common side effect with SSRIs.

Sedation

Although these agents are primarily thought to be activating agents, sedation is considered a common side effect. Rosenberg et al. (1999) reported that 5% of

the 20 OCD patients treated with paroxetine 10–60 mg/day experienced sedation. Moreover, changing the timing of drug administration often fails to affect the sedation (Cole and Bodkin, 1990). Nonetheless, we recommend that if a patient experiences sedation while being treated with an SSRI, administration should be tried before bedtime.

Dreaming

Having abnormal dreams is a frequent side effect of SSRIs. Early and sustained dreaming in four dysthymic adult patients on fluoxetine has been reported (Markowitz, 1991). These patients spontaneously described these dreams as “newly” vivid. Interestingly, this intensification of dreams was not experienced as unpleasant, but more as a curiosity. The dreams became more memorable, although they did not change in content or form. The dreams returned to baseline in two patients who discontinued fluoxetine and subsequently increased in one case upon rechallenge with the medication. According to the investigator, this “vibrant” dreaming preceded antidepressant response.

It is known that SSRIs suppress REM sleep less than do most antidepressants (Bernstein, 1988). In addition, SSRIs produce less sedation than do other serotonergic agents, such as trazodone (Scharf and Sachais, 1990). While this fact may explain the increased dream intensity and better dream recall on awakening, polysomnographic studies (Bernstein, 1988; Nicholson and Pascoe, 1988) have not described this dream phenomenon. Armitage and colleagues (1997) have reported that SSRIs can increase REM sleep in children and also adolescents, resulting in more vivid dreams. There is a paucity of other available literature on this subject.

Motor Restlessness/Akathisia/Abnormal Motor Movements

Riddle and colleagues (1990b) observed motor restlessness, a relatively common side effect of SSRIs, in 46% of children and adolescents treated with fluoxetine, 20–40 mg/day, for depressive or obsessive-compulsive symptoms (Cole and Bodkin, 1990). Indeed, three children with ADHD actually showed an exacerbation of symptoms while on fluoxetine.

Serotonin has a significant inhibitory effect on dopaminergic neurons (Baldessarini and Marsh, 1990). This inverse relationship of serotonin and dopamine is also evident in OCD where Marazziti et al. (1992) reported reduced 3H-imipramine binding sites, suggesting presynaptic dysfunction of the serotonergic system and increased sulfotransferase activity, an enzyme critically involved in the catabolism of catecholamines such as dopamine. Korsgaard et al. (1985) found that SSRIs reduce amphetamine-induced stereotypes and increase dystonia associated with haloperidol. Parkinsonian side effects and akathisia have been reported in patients treated with SSRIs (Bouchard et al., 1987; Lipinski et al., 1989; Jones-Fearing, 1996; Leo, 1996; Leonard et al., 1997; Gill et al., 1997;

Bates and Khin-Maung-Zaw, 1998; Boyle, 1999). Lipinski et al. (1989) further suggest that SSRI treatment results in serotonergic inhibition of dopaminergic neurotransmission resulting in SSRI-induced akathisia.

Neuromuscular restlessness can approximate neuroleptic-induced akathisia and may respond to dosage reduction or temporary benzodiazepine therapy (Arana and Hyman, 1991). Clonazepam, 0.25–0.5 mg b.i.d., has proved useful in treating this akathisia-like syndrome (Arana and Hyman, 1991). As mentioned, the incidence of akathisia with fluoxetine use is being reported more frequently. The reader is also referred to a comprehensive review by Wilens and colleagues (1998) for distinguishing disinhibition vs. manic/hypomanic symptoms in children and adolescents.

Dry Mouth

Dry mouth can be a common side effect of SSRIs. It was noted in 40% of 115 depressed adolescents on fluoxetine (Mann et al., 1992).

Male Sexual Dysfunction

In adults, male sexual dysfunction, primarily ejaculatory delay, is considered a relatively common side effect of SSRIs. Pfizer Inc., the manufacturer of sertraline (Zoloft), has reported that sexual dysfunction occurred in 15.5% of males treated with sertraline, as opposed to 2.2% treated with placebo (Physicians' Desk Reference, 2001). Anorgasmia has been reported to affect approximately 5% of patients treated with fluoxetine (Herman et al., 1990). This side effect may respond to cyproheptadine taken PO 4–8 hours before the sexual activity is planned (Kaplan and Sadock, 1991). Ejaculatory disturbances have been reported in 13% of patients treated with paroxetine vs. 0% with placebo (Physicians' Desk Reference, 2001). Other male genital disorders were observed in 10% of patients treated with paroxetine and 0% of patients treated with placebo. Sexual dysfunction may be somewhat less when the SSRI fluvoxamine is used, although abnormal ejaculation was observed in 8% of patients treated with fluvoxamine as compared to 1% of those treated with placebo. Sexual dysfunction may also be less common in patients treated with citalopram, although 6% of patients treated with citalopram exhibited an ejaculation disorder as compared to only 1% of patients treated with placebo.

There are no data on children and adolescents, although it is believed that this side effect is less common in this population. Nonetheless, the practicing clinician must be aware of this side effect, particularly when administering sertraline to adolescent (and possibly sexually active) males.

Emergence of Self-Destructive Phenomena

Teicher and colleagues (1990a, 1990b) published reports that generated a great deal of publicity and controversy in the scientific and lay communities. They

suggested that the emergence of intense suicidal preoccupation in six adult patients may have been induced by fluoxetine. The evidence for this was far from conclusive, since the majority of these patients had previously experienced suicidal ideation and had been treated with a variety of psychotropic medications. Prior to this report, Gorman and colleagues (1987) had noted that, in an open trial of fluoxetine in the treatment of panic attacks, two nonresponders who dropped out of the study because of adverse side effects became depressed and developed suicidal ideation. Only one of the two had a prior history of depression.

King and associates (1991) reported that self-injurious ideation or behavior appeared *de novo* or was intensified in six patients, 10–17 years of age, among 42 children and adolescents receiving fluoxetine for OCD. Before receiving fluoxetine, four of the patients had significant risk factors for self-destructive behavior, including depression and suicidal ideation or attempt. Indeed, several recent reports have failed to show any association between fluoxetine treatment and suicidality (Ayd, 1990; Beasley et al., 1991; Fava and Rosenbaum, 1991). Boulos and colleagues (1992) treated 15 adolescents with treatment-resistant depression with fluoxetine doses of 5–40 mg/day for 6–7 weeks without observing any increase in suicidal ideation, suicide gestures, or self-inflicted injuries either in the month prior to or during the fluoxetine treatment period. Rosenberg et al. (1999) reported the new emergence of suicidal ideation in 1 of 20 (5%) pediatric OCD patients treated with paroxetine. Patients enrolled in this study had no previous history of MDD, although one had dysthymia. This patient was maintained on paroxetine and subsequently responded well to an increased dose of paroxetine in combination with psychosocial and family intervention. He has continued to do well over the past 2.5 years without reemergence of suicidal ideation.

It should be noted that depressed patients have a significantly increased rate of attempting and completing suicide, with 10–15% actually killing themselves and significantly more making suicidal gestures and attempts. Bipolar depression is associated with an even higher suicide risk, up to 20%. Depression is a serious illness with life-threatening consequences. Moreover, other anxiety disorders for which SSRIs are often used also have increased risk for development of MDD. Two thirds of OCD patients, for example, will experience a major depressive episode during their lifetime. Nonetheless, as with all psychotropic medications, careful monitoring for toxicity, lack of treatment efficacy, and worsening of the depression is most important.

Behavioral Disinhibition/Hyperactivity/Hypomania/Mania

Social disinhibition may be a relatively common side effect of SSRI treatment. Six of 24 children and adolescents treated with fluoxetine at doses of 20–40 mg/day experienced this side effect (Cole and Bodkin, 1990). Behavioral side effects characterized by a subjective sensation of excitation were also observed in three

of 24 patients treated with fluoxetine 20–40 mg/day. Rosenberg and colleagues (1999) observed hyperactivity/behavioral disinhibition in 30% of 20 pediatric OCD patients treated with paroxetine 10–60 mg/day. However, the medication did not have to be discontinued in any of the patients as reduction in dosage and giving children time to become tolerant to paroxetine led to the remission of this side effect. We recommend discussing these side effects with parents and the child being treated with the SSRIs beforehand as this side effect is often transient. Careful explanation as to differences between these phenomena and hypomania and mania is, of course, critical (discussed below). It is also worth pointing out that many patients treated with SSRIs including patients with anxiety disorders, OCD, and severe depressions may be remarkably inhibited at baseline and it is important not to confuse healthy childhood exuberance with a medication side effect. For example, if parents are concerned about behavior that is not typical in the child but which they might excuse saying, “That’s just Joe or Jane being Joe or Jane,” but which is surprising in their child who has been previously so inhibited and withdrawn, this may actually be a “good” outcome although as with any child appropriate parental counseling about tempering behavior is indicated.

Although the manic switch rate is about 11% in adult patients with bipolar disorder treated with TCAs but only 4% with the SSRIs (Peet, 1994; Bunney et al., 1972,1978; Wehr and Goodwin, 1979; Lensgraf and Favazza, 1990), SSRIs have been associated with induction of hypomania and mania in children and adolescents. This may be a particular concern in pediatric MDD patients who may have a higher risk of ultimately developing bipolar disorder. However, it is not clear at present how to discriminate nonpsychotic pediatric MDD patients who will develop bipolar disorder from those who will not. MDD with psychosis in children clearly carries an increased risk for bipolar disorder so that caution is indicated when prescribing these medications in such patients (See also Chapter 12, Antipsychotics for treatment of MDD with psychosis). OCD patients are often treated with higher doses of SSRIs which may also increase the risk for manic switch (Dorevitch et al., 1993; Mundo et al., 1993).

Various reports describing mania induced by fluoxetine have surfaced (Settle and Settle, 1984; Sholomskas, 1990; Steiner, 1991; Stoll et al., 1991; Turner et al., 1985; Wong et al., 1974; Hon and Preskorn, 1989; Lebegue, 1987; Nakra et al., 1989; Chouinard and Steiner, 1986; Feder, 1990). Fluoxetine induced mania has been reported in adolescent patients with ADHD and MDD (Achamallah and Decker, 1991; Jain et al., 1992; Rosenberg et al., 1992; Venkataraman et al., 1992; Boulos et al., 1992; Colle et al., 1994; Fairbanks et al., 1997). Go and colleagues (1998) studied 20 pediatric patients 11–17 years of age with OCD and mood disorders treated with serotonin reuptake inhibitors. Six of the patients (30%) developed hypomanic or manic symptoms. Five of 15 patients treated with fluoxetine and 1 patient treated with sertraline developed hypomanic or manic

symptoms. It should be noted that symptoms which included marked impulsivity, grandiosity, pressured speech and extreme behavioral disinhibition were described as “not resembling” akathisia or activation of behavior. Moreover, these symptoms were observed even with very conservative dosing regimens (2–5 mg/week) and maximum daily doses of fluoxetine not exceeding 40 mg. In fact, one OCD patient became manic on fluoxetine 10 mg/day. Thus, any patient being treated by an antidepressant must be carefully monitored for the evolution of mania/hypomania. The reader is again referred to the comprehensive review by Wilens and colleagues (1998), which includes very practical advice in differentiating between mania/hypomania and disinhibition or increased activation.

Rash/Allergic Reactions

Patients on SSRIs may develop allergic reactions to the medication, although this may sometimes be due to the dye in the tablet rather than the SSRI itself. In the initial studies on fluoxetine, 4% of the patients developed a rash and/or urticaria (Physicians' Desk Reference, 2001), and almost one third were withdrawn from treatment as a result. All patients recovered completely upon discontinuation of fluoxetine, although in some cases, treatment with antihistamines or steroids was required. Any patient being treated with an antidepressant must be carefully monitored for hypersensitivity reactions. Fluvoxamine, sertraline, fluoxetine, and paroxetine have also been reported to possibly be involved in rarely triggering the Stevens-Johnson syndrome (Goldman, 2001).

Seizures

Twelve patients among more than 6000 SSRI-treated patients (0.6%) experienced events described as seizures, a rate comparable to that observed with other antidepressants (Physicians' Desk Reference, 2001). Thus, it is important that SSRIs be introduced with care in patients with a history of seizure disorder. Although antidepressants have been reported to lower the seizure threshold, this does not preclude their use, particularly for the treatment of disorders for which SSRIs are efficacious. Ensuring that the patient is on a stable anticonvulsant regimen, adjusting the dose accordingly in the event of impaired seizure control, is recommended.

Hair Loss

A case of severe hair loss in an adult treated with fluoxetine was reported by Jenike (1991). In a multicenter trial of approximately 600 patients, he reported a rate of less than 1%, suggesting that true hair loss as a fluoxetine side effect is negligible (Jenike, 1991). In the study by Boulos and associates (1992) in which 15 depressed adolescents and young adults were treated with fluoxetine,

2 patients reported hair thinning. This effect was transient, however, and did not require medication withdrawal. This effect was not reported in 20 pediatric OCD patients treated with paroxetine 10–60 mg/day (Rosenberg et al., 1999).

Anticholinergic Effects

The SSRIs have essentially no anticholinergic effects. In vitro, paroxetine may have more anticholinergic effects than other SSRIs, although the clinical relevance of this phenomenon is uncertain.

Cardiovascular Effects

Most notable about the SSRIs is their general lack of adverse cardiovascular side effects. Mortality is quite rare even in cases of massive overdose (Gutgesell et al., 1999). The American Heart Association does not recommend any specific cardiovascular monitoring for SSRI monodrug therapy. No significant ECG changes have been reported with fluoxetine, although it can change concentrations and levels of protein-bound medications such as digoxin and warfarin, necessitating their dosage adjustment. Amsterdam and colleagues (1999) found that fluoxetine is not associated at a rate above placebo with peripheral hypertension (approximately 1%). They examined sitting and systolic and diastolic blood pressure, pulse rate, and rate of sustained hypertension in 796 adults with MDD (mean age 40 years \pm 11 years) who were administered fluoxetine 20 mg/day for up to 3 months. There was relatively modest significant reduction in sitting and standing systolic and diastolic blood pressures in patients with fluoxetine treatment. Pretreatment diastolic blood pressure < 60 mm Hg (32 of 796 patients) experienced a modest elevation in mean diastolic blood pressure. Conversely, patients with a pretreatment diastolic blood pressure \geq 90 mm Hg and <95 mmHg (57 of 796 patients) experienced a modest decrease in mean diastolic blood pressure. It is important to point out that patients with previously diagnosed and stable cardiovascular disease including hypertension (35 of 796 patients) experienced no significant change in systolic or diastolic blood pressure. Of patients treated with fluoxetine in this study, 1.7% exhibited sustained hypertension for three or more consecutive office visits. This rate is lower than that reported in patients receiving venlafaxine (4.8%) (see Chapter 10) and comparable to rates seen with placebo (2.1%). The authors concluded that there was a very low rate of sustained hypertension (<2%) with short-term therapy (up to 12 weeks) with fluoxetine.

Brain Development

The long-term impact of SSRIs on brain development and function are unknown. These are frequent concerns of the child and family and clinicians alike in whom

SSRI treatment is being considered. It should be noted that the illnesses for which these medications are prescribed are quite serious, with substantial risk for morbidity and mortality, so a risk-benefit analysis is indicated, particularly if additional investigation confirms the safety and efficacy of these medications. Nonetheless, long-term study is warranted to address concerns about the medication's effect on brain development and other potentially unknown side effects. In nonhuman primates, for example, Goldman-Rakic and Brown (1982) demonstrated that dopamine and norepinephrine synthesis and storage capacity continue to develop throughout childhood and adolescence and into early adulthood, whereas serotonergic synthesis and storage achieves adult levels much earlier in development. In adult rodents, chronic fluoxetine treatment has been found to upregulate 5-HT uptake sites and 5-HT₂ receptors (Hrdina and Vu, 1993). Prenatal exposure of rats to fluoxetine has also resulted in reduced litter size at higher doses of fluoxetine but does not appear to impact performance or motor activity (Vorhees et al., 1994). It should be noted, however, that Cabrera and Battaglia (1994) found that prenatal fluoxetine exposure led to dramatic biochemical and functional alterations in the serotonergic system that were only evident later in the rat's maturation. This may be consistent with findings of McCann and colleagues (1994) in which chronic fluoxetine treatment results in upregulation of 5HT uptake sites and 5-HT₂ receptors in the brains of adult rats. Further study of the impact of SSRI treatment on developing brain in humans is clearly warranted. Newer and more sophisticated brain imaging techniques, including positron emission tomography and magnetic resonance spectroscopy, allow for the direct, noninvasive evaluation of the impact of psychotropic medication on brain anatomy, function, and chemistry.

OVERDOSE/TOXICITY

In contrast to the TCAs, overdoses with SSRIs have a low lethality (Riddle et al., 1989; Feierabend 1995). In contrast to the TCAs, SSRIs do not typically effect cardiac conduction (Walkup, 1994). This makes it easier for clinicians to prescribe these agents for impulsive patients suffering from a wide variety of psychopathologic processes who are prone to making suicidal gestures. The chances of surviving without severe toxicity and sequelae are far greater with the SSRIs.

There has been only one report of a lethal overdose when fluoxetine was taken by itself, but there have been several reports of lethal overdose when it was taken with other psychotropic drugs. Thus, it is essential in cases of SSRI overdose that the clinician determine what other drugs were taken. Symptoms of SSRI overdose can include agitation, nervousness, restlessness, nausea, vomiting, insomnia, seizures, hypomania/mania, and other signs of CNS excitation (Physicians' Desk Reference, 2001).

The management of SSRI overdose involves establishing and maintaining an airway to ensure adequate oxygenation and ventilation (Physicians' Desk Reference, 2001). Activated charcoal with sorbitol may be more effective than emesis or lavage. It is important that cardiac and vital signs be monitored during the acute period of the overdose. When managing SSRI overdose, it is essential that the possibility of multiple drug involvement be considered. For example, if fluoxetine and a TCA are ingested together in overdose, TCA levels and resultant cardiac and other side effects may be greatly exacerbated. Thus, in addition to questioning the patient and family, urine and serum drug screens must be performed to adequately gauge what substances the patient has ingested.

There have been no reported deaths with paroxetine, sertraline, fluvoxamine, or citalopram.

ABUSE

There is little potential for abuse with these agents.

DRUG INTERACTIONS

See Table 7.

AVAILABLE PREPARATIONS

See Table 8.

INITIATING AND MAINTAINING TREATMENT

Prior to initiating treatment, children and adolescents should have a physical examination, with special attention to vital signs, height, and weight. As these agents do cross the placenta, a pregnancy test and evaluation for adequate contraceptive use may be warranted in females of childbearing age. It is also advisable to discern the sexual history of adolescent males, since these agents occasionally have been reported to cause anorgasmia and ejaculatory problems in adults. This may be an important compliance issue. Extensive laboratory testing is generally unnecessary. For example, in the NIMH-funded multicenter Treatment for Adolescents with Depression Study (TADS) using the SSRI fluoxetine, no laboratory screening other than a pregnancy test for adolescent females is included in the protocol. It should be noted that industry-sponsored studies continue to perform ECG and extensive laboratory analysis during the course of their SSRI studies. However, in routine clinical practice, such testing is typically not performed unless there is a specific clinical indication.

TABLE 7 Drug Interactions—SSRIs^a

Coadministration can result in dangerous side effects for patients on:

MAOIs
 Heterocyclics
 L-Tryptophan
 Lithium
 Hypericum (St. John's wort)

When used with these agents, increases plasma levels of:

Heterocyclic antidepressants
 Benzodiazepines (e.g., diazepam)

Coadministration can result in decreased therapeutic effect of:

Buspirone

* Side effects and adverse drug-drug interactions may be more likely and severe in patients treated with fluoxetine than the other SSRIs due to its much longer half-life.

It is also important to take a careful substance-abuse history. The patient and family need to be warned about the potential danger of taking SSRIs in combination with drugs and alcohol. A case of mania associated with fluoxetine-marijuana use has been reported in an adult (Stoll et al., 1991).

Careful screening for risk for mania/manic switch is also indicated. Pediatric MDD with psychosis may carry an especially high risk for evolving into mania; thus, SSRIs should be used with caution in such patients. Other indicators of pediatric MDD patients who will become bipolar are not clear at present, underscoring the need for very careful monitoring and follow-up in all children and adolescents treated with SSRIs.

If the patient is on another psychotropic agent, particularly a TCA, it should be tapered off prior to starting an SSRI, particularly fluoxetine, since fluoxetine can dramatically increase TCA (and other medication) blood levels. In those cases where it is decided to use an SSRI with a TCA, careful monitoring of TCA levels and vital signs and cardiograms is indicated. The measurement of SSRI levels is not helpful in assessing or targeting clinical response.

It is also important to ask the patient and family about use of over-the-counter herbal remedies for treatment of depressive, anxiety, and other neuropsychiatric symptoms. Use of these medications in adults and children alike has increased significantly in recent years (see Chapter 17). There is very little data on herbal medications in children and adolescents, particularly with regards to drug-drug interactions, side effects, and safety/efficacy. Hypericum (St. John's wort), for example, should not be prescribed concurrently with an SSRI because of risk of serotonin syndrome. If the decision is made to prescribe an SSRI in a

TABLE 8 Available Preparations and Costs of SSRIs

Drug	Commercially available preparations	Dosage forms	Average cost/day
Fluoxetine	Prozac	10 mg scored, 20 mg pulvules. Liquid preparation contains fluoxetine hydrochloride; liquid contains 20 mg/5 mL.	\$1.44
	Sarafem ^a	FDA-approved. Not yet released.	Pending release
Sertraline	Zoloft	25, 50, 100 mg scored tablets.	\$0.54
Fluvoxamine	Luvox	25 mg unscored; 50, 100 mg scored.	\$3.68
Paroxetine	Paxil	10, 30, 40 mg unscored, 20 mg scored. Liquid preparation, each 5 mL contains 10 mg paroxetine.	\$2.79
Citalopram	Celexa	10, 20, 40 mg scored tablets. Liquid preparation, each 5 mL contains 10 mg citalopram.	\$2.67

^a Not marketed as Prozac because of Eli Lilly's concerns that there may be stigma associated with the brand name Prozac. Sarafem and Prozac are identical except for having different colored capsules (Clinical Psychiatry News, August 2000).

patient taking St. John's wort, the herbal remedy should be discontinued prior to initiating the SSRI trial. We also advise checking with patients and families during the course of treatment to make sure they have not started taking a herbal remedy during the course of therapy.

Because of the substantial publicity regarding fluoxetine and its alleged association with suicidal behavior, we recommend confronting this issue with the patient and family if it is decided the patient may benefit from this agent. Emphasis on close monitoring and active participation by the patient and family so that any behavioral side effects are immediately noted and acted upon can provide reassurance. We have found it helpful to give parents and patients a drug information sheet on fluoxetine (as well as other psychotropic medications) using nonmedical jargon. It describes what fluoxetine is, how the medication can help, how the physician will monitor treatment, what the side effects are, and the possi-

ble drug interactions (Table 9). In our experience, directly confronting the issue frequently reassures the patient and family.

Patients on SSRIs should be monitored at each visit for involuntary movements and CNS excitation (mania/hypomania). It must be emphasized that the SSRIs may induce increased activity without mania or hypomania (Wilens et al., 1998). It is also advisable to record height and weight at regular 3- to 4-month intervals. Children and adolescents should have an annual physical examination.

It should also be noted that there are liquid preparations for fluoxetine, paroxetine, and citalopram. This may be particularly helpful in younger children with problems swallowing pills. The liquid preparation of paroxetine is orange colored with an orange flavor, while the liquid preparation of citalopram has a mint flavor. Liquid preparations also allow for additional flexibility of dosage titration. For example, each 5 mL of the liquid preparation of paroxetine contains 10 mg of drug. Thus, it is possible to initiate doses of 5 mg/day (2.5 mL of the liquid preparation).

Treatment Duration

There are no firm guidelines as to how long treatment with SSRIs in children and adolescents should last. Once treatment response is obtained with an SSRI, we recommend the patient being maintained on the dose of SSRI that achieved remission of symptoms for at least 12 months. A reassessment at that point is indicated. As when an SSRI is initiated, tapering of medication should be gradual to minimize withdrawal symptoms and/or reemergence of symptoms. The reader is also referred to the guidelines on treatment duration (discussed in Chapter 8).

Withdrawal

As with the TCAs, withdrawal and flu-like syndromes can occur when the SSRIs are abruptly discontinued. There may also be increased risk of symptoms re-emerging when SSRIs are abruptly withdrawn. This may be more common with shorter-acting SSRIs like paroxetine where anecdotal reports have noted withdrawal symptoms in patients missing a single dose of medication. Thus, tapering is necessary, and some patients may require especially gradual tapering to minimize withdrawal and/or symptom recurrence. It should be noted, however, that in the event of an emergency, these medications can be immediately discontinued. In contrast to alcohol, benzodiazepines, and the barbiturates, the SSRIs are not physically addictive. While patients cannot die from SSRI withdrawal, it can be unpleasant, so in nonemergent situations, we advise gradual tapering of the medication.

There are now five SSRIs (paroxetine, fluoxetine, citalopram, fluvoxamine, and sertraline) routinely used in the United States. Thus, it has become important

TABLE 9 Parent Information on Prozac*What is Prozac?*

Prozac (generic name fluoxetine) is a new medication that was developed as an antidepressant. It is chemically different from other antidepressant medications, and works in a different way. It is available in capsules (called Pulvules) and in a liquid form.

How can this medication help?

Because Prozac is so new, there has not been much research on its use with children and adolescents, although a great deal is known about its use with adults. It is being used on a trial basis to help children and adolescents who suffer from depression, OCD, or obsessions or compulsions as part of Tourette's syndrome. It may be effective for patients who have tried other medications, but do not get better or develop side effects.

How will the doctor monitor this medicine?

The doctor will want you to have regular visits to evaluate how Prozac is working, to adjust the dose, to watch for side effects, and to see if other treatment is needed.

What side effects can this medicine have?

Any medication may have side effects. Because each patient is different, your doctor will work with you to get the most positive effects and the fewest negative effects from the medicine. This list may not include rare or unusual side effects. Please talk to the doctor if you suspect the medicine is causing a problem. In general, Prozac has fewer and less troublesome side effects than other antidepressants.

Common nuisance side effects:

Nausea; weight loss or gain; anxiety or nervousness; insomnia (trouble sleeping); excessive sweating; headaches.

Some persons may become restless or agitated, with increased activity and rapid speech, an uncomfortable feeling of being "speeded up." This is worse at first, and may improve if the dose is lowered.

There has been a lot of publicity suggesting that Prozac may cause suicidal thoughts. This is very rare, if it occurs at all, and may be due to the depression itself rather than Prozac. In any case, if suicidal thoughts or actions appear or worsen, call the doctor right away.

What else should I know about this medicine?

It can be dangerous to take Prozac at the same time or within 5–6 weeks of taking a type of antidepressant called an MAO inhibitor (Nardil, Parnate, or Marplan).

Prozac interacts with many other medications. Be sure each doctor knows all of the medications that are being taken, or have been taken in the past several months.

Source: Dulcan, M.K. (1992). Information for parents and youth on psychotropic medications. *J Child Adolesc Psychopharmacol*, 2(2), 81–101.

TABLE 10 Dosage and Administration of SSRIs in Pediatric Neuropsychiatric Conditions

Fluoxetine

- Initiate dose at 5–10 mg/day
- Increase dose by 5–10 mg increments every 2–4 weeks to a maximum dose of 80 mg/day
- Lowest effective dose with minimal toxicity should be prescribed
- Medication trial of at least 12 weeks necessary before treatment resistance can be determined
- If treatment response occurs, must be maintained on medication dose that achieved symptom resolution for 12 months
- Gradual tapering (5–10 mg/day decrements every 2–4 weeks) is indicated to minimize risk of withdrawal and/or re-emergence of symptoms
- Careful monitoring required

Sertraline

- Initiate dose at 25 mg/day
- Increase dose by 25 mg/day increments every 2 weeks to a maximum of 200 mg/day
- Lowest effective dose with minimal toxicity should be prescribed
- 12 week trial is necessary before treatment resistance can be determined
- If treatment response occurs, must be maintained on medication dose that achieved symptom resolution for 12 months
- Gradual tapering (25 mg/day decrements every 2 weeks) is indicated to minimize risk of withdrawal and/or re-emergence of symptoms
- Careful monitoring required

Fluvoxamine

- Initiate dose at 25 mg/day
- Increase dose by 25 mg/day increments every 2 weeks to a maximum dose of 300 mg/day
- Lowest effective dose with minimal toxicity should be prescribed
- 12 week trial is necessary before treatment resistance can be determined
- If treatment response occurs, must be maintained on medication dose that achieved symptom resolution for 12 months
- Gradual tapering (25 mg/day decrements every 2 weeks) is indicated to minimize risk of withdrawal and/or re-emergence of symptoms
- Careful monitoring required

Paroxetine

- Initiate dose at 10 mg/day
- Increase dose by 10 mg/day increments every 2 weeks to a maximum dose of 60 mg/day
- Lowest effective dose with minimal toxicity should be prescribed
- 12 week trial is necessary before treatment resistance can be determined
- If treatment response occurs, must be maintained on medication dose that achieved symptom resolution for 12 months

TABLE 10 Dosage and Administration of SSRIs in Pediatric Neuropsychiatric Conditions

- Gradual tapering (10 mg/day decrements every 2 weeks) is indicated to minimize risk of withdrawal and/or re-emergence of symptoms
- Careful monitoring is required

Citalopram

- Initiate dose at 10 mg/day
- Increase dose by 10 mg increments every 2 weeks to a maximum dose of 60 mg/day
- Lowest effective dose with minimal toxicity should be prescribed
- 12 week trial is necessary before treatment resistance can be determined
- If treatment response occurs, must be maintained on medication dose that achieved symptom resolution for 12 months
- Gradual tapering (10 mg/day decrements every 2 weeks) is indicated to minimize risk of withdrawal
- Careful monitoring required

to know whether lack of efficacy and/or intolerance to one SSRI means that patients will be refractory and/or intolerant to all of the others. Recent findings in adults suggest that this does not happen (Jenike, 1991). A multicenter trial that studied how patients who experienced intolerable side effects from fluoxetine would respond to sertraline included 100 patients who met DSM-III-R criteria for MDD and who had discontinued fluoxetine because of side effects (Jenike, 1991). After a washout of at least 4 weeks following fluoxetine discontinuation and an additional one-week single-blind placebo period, patients were switched to open treatment with sertraline. They began treatment with 50 mg per day, and, based on their response, doses were titrated upward as necessary. The maximum daily dose was 200 mg/day. Weekly assessments included administration of the Hamilton Depression Inventory and the recording of adverse effects and laboratory values. Based on an interim analysis of the first 60 patients completing at least 6 weeks of treatment, 75% were rated as being very much or much improved. These results suggest that, as with the TCAs, patients who are unable to tolerate one SSRI may be treated successfully with another.

Finally, to provide information on the use of sertraline for the continuation of maintenance therapy, Turner and associates (1992) reported that, in a placebo-controlled study of maintenance sertraline therapy for 44 weeks, sertraline helped to prevent the relapse of an index episode of depression and the recurrence of further episodes, with few side effects. Thus, to reiterate, we recommend maintenance therapy with an SSRI for 12 months at the dose at which symptom recurrence occurred prior to tapering and discontinuing the medication.

CLINICAL PRACTICE

For dosing and administration, see Table 10. For lithium augmentation of SSRI nonresponsiveness, see Chapter 13. For the use of benzodiazepines see Chapter 15.

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10

Novel (Atypical) Antidepressants

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The selective serotonin-reuptake inhibitors (SSRIs) are now the drugs of choice for the treatment of juvenile depression (Emslie et al., 1998). Together with fluoxetine, other SSRIs currently prescribed for children and adolescents with mood disorders, sertraline (Zoloft™), paroxetine (Paxil™), fluvoxamine (Luvox™) and citalopram (Celexa™), are discussed in detail in Chapter 9 of this textbook. Novel antidepressants [not chemically related to the tricyclics (TCAs) or the SSRIs] such as bupropion (Wellbutrin™), trazodone (Desyrel™), nefazodone (Serzone™), mirtazapine (Remeron™), and venlafaxine (Effexor™) have been prescribed to children and adolescents for unlabeled (non-FDA-approved) indications. Their psychopharmacological profile and relevant pediatric studies are summarized in this chapter. Together with these agents, we will also discuss the adjuvant treatment of depression with thyroid hormones.

TRAZODONE

Trazodone is an atypical antidepressant chemically unrelated to the TCAs. Although trazodone is commonly referred to as a serotonin (5-hydroxytryptamine; 5-HT) uptake inhibitor, its most important pharmacological effect is the antagonism of 5-HT₂/1C receptors (Marek et al., 1992). Trazodone is approved for the

treatment of major depressive disorder (MDD) in adults (AHFS, 2000). It is best known for its sedative effect. Trazodone has been reported to increase total sleep time, decrease the number of nighttime awakenings and decrease REM sleep, without decreasing stage IV sleep (Mouret et al., 1988). There are very limited data in children and adolescents (Wiener, 1991). In this section we will briefly discuss some of its possible applications in this population.

Chemical Properties

Trazodone is rapidly absorbed from the gastrointestinal (GI) tract following oral administration and achieves peak plasma concentrations in 1–2 hours (AHFS, 2000). These peak plasma levels are achieved more rapidly on an empty stomach. It has a relatively short half-life of 6–11 hours. Trazodone is metabolized by the liver, and its active metabolite, *m*-chlorophenyl-piperazine, is excreted by the kidneys (AHFS, 2000).

Indications

Given the dearth of controlled data, we do not recommend the routine use of trazodone in children and adolescents with MDD or other disorders. Nevertheless, the following are (pediatric) reports of interest.

Levi and Sogos (1997) recently treated a mixed group of 80 pediatric outpatients (ages 9–13) with MDD, comorbid with oppositional defiant disorder, generalized anxiety disorder, and learning disorders. These youngsters received weekly blind ratings while taking 75 mg of trazodone for 4 months. Trazodone was reportedly safe and effective for over 50% of the sample (Levi and Sogos, 1997). The comorbidity with oppositional defiant disorder was associated with poorer response (Levi and Sogos, 1997).

A recent retrospective review of adolescents with MDD and insomnia receiving fluoxetine (average 20 mg/day), trazodone (71 mg/day), or a fluoxetine-trazodone combination (fluoxetine 29 mg/day, trazodone 68 mg/day) examined the relative effectiveness of each drug in relieving insomnia (Kallepalli et al., 1997). Although the mean time to resolution of insomnia was significantly faster in adolescents treated with trazodone, the median time to insomnia resolution was 2 days in the trazodone group and 4 days in the fluoxetine group, questioning the clinical significance of the statistical finding (Kallepalli et al., 1997).

Zubieta and Alessi (1992) conducted an open trial of trazodone in the treatment of severe behavioral disturbances in 22 hospitalized children diagnosed with disruptive behavioral and mood disorders previously unresponsive to other treatments. Assessed by overall clinical criteria, 13 children (67%) were considered responders to a mean dose of 185 ± 117 mg/day (given t.i.d) for a mean of 27 ± 20 days. Aggressive, impulsive behaviors were the symptoms most frequently improved by trazodone. One patient reported painful erections. The most

frequent side effect was orthostatic hypotension. Three nonresponders worsened in symptomatology (Zubieta and Alessi, 1992).

The combination of haloperidol and trazodone was recently evaluated in an open-label trial of 10 patients with chronic tics and Tourette's disorder. A mean reduction of symptoms of 59% was found, with a statistically significant difference between the baseline and endpoint treatment conditions, suggesting a potential for using lower doses of haloperidol for the treatment of tics in children (Saccomani et al., 2000).

Ten adolescents with bulimia nervosa were treated in an open-label, flexible-dose study of trazodone for a mean duration of 7 weeks, at a mean maximum dose of 410 mg (Solyom et al., 1989). The authors reported that the number of binge-eating and vomiting episodes was significantly decreased (Solyom et al., 1989). Pretreatment versus posttreatment mean weight was essentially unchanged. Mild side effects noted were morning drowsiness and headache (Solyom et al., 1989).

A recent study also suggested that trazodone may be effective and safe in the acute withdrawal from methadone (Pozzi et al., 2000).

All of the above reports await replication by controlled studies. In the meantime, the use of trazodone in children and adolescents with MDD is at best recommended for female youngsters who have failed other first-line agents and present with insomnia as one of their salient clinical features. Other disorders for which trazodone does not have FDA approval, i.e., bulimia, tics, impulsive-aggressive behavior, await further replication in pediatric populations before off-label treatment can be endorsed.

Side Effects

Priapism

Priapism is a potential side effect of trazodone therapy, resulting in a prolonged penile erection (Thompson et al., 1990). The occurrence of priapism constitutes a medical emergency since it may result in permanent erectile dysfunction even when prompt treatment is received. Priapism may be secondary to trazodone's α -adrenergic blocking properties (Thompson et al., 1990). Adolescent males patients should be questioned concerning prior occurrence of prolonged erections, since a past history of delayed detumescence has been reported in approximately 50% of subsequent cases of priapism (Thompson et al., 1990). This potential side effect precludes the enthusiastic endorsement of trazodone therapy in male adolescents.

Orthostatic Hypotension

In adults, orthostatic hypotension secondary to trazodone can occur (AHFS, 2000). This is believed to be mediated, in part, by its α_1 -adrenergic antagonism

(Davis and Glassman, 1991). This side effect may be less common in children and adolescents, although there are limited data on trazodone's efficacy and toxicity in this population (AHFS, 2000).

Other Side Effects

Sedation and dizziness are common, often transient side effects of trazodone (Newton, 1981). Conversely, an acute dystonic reaction has also been described in an adolescent taking trazodone (Tesler-Mabe, 1998). Gastrointestinal disturbances such as nausea and vomiting can be minimized by taking the medication in divided doses and with meals (AHFS, 2000). Taking the medication with meals slows its absorption and appears to decrease the incidence of dizziness or lightheadedness (AHFS, 2000). Although trazodone had little antiarrhythmic effects in preclinical and clinical trials (Janicak et al., 2001), there has been a report that trazodone aggravated arrhythmias in patients with preexisting ventricular conduction disease (Vitulo et al., 1990). Anticholinergic side effects are generally not seen with trazodone.

Dosage and Administration

Trazodone is available in 50, 100, 150, and 300 mg tablets (Desyrel[®]; Dividose[®]; Apothecon) (AHFS, 2000). For the treatment of MDD, the usual initial adult dosage is 150 mg daily given in divided doses, taken shortly after a meal (AHFS, 2000). Total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach (AHFS, 2000). Dosage may be increased by 50 mg/day every 3 or 4 days, depending on therapeutic response and tolerance. The maximum dosage for outpatients usually does not exceed 400 mg daily (AHFS, 2000).

Drug Interactions

Fluoxetine may inhibit the hepatic metabolism of trazodone during concomitant trazodone and fluoxetine therapy, hence increasing plasma trazodone concentrations and causing adverse effects associated with trazodone toxicity (AHFS, 2000). Although trazodone does not interfere with catecholamine uptake, both monoamine oxidase inhibitor (MAOI) and trazodone possess serotonergic activity, therefore a serotonin syndrome may occur during concurrent therapy (AHFS, 2000). Because trazodone can cause orthostatic hypotension, concomitant administration with clonidine may require a reduction in dosage of the latter agent (AHFS, 2000).

BUPROPION

Bupropion is an atypical antidepressant unrelated to the TCAs. It is FDA-approved for the treatment of adults with MDD (AHFS, 2000). Limited data are

available in children and adolescents (Conners et al., 1996; Popper, 1997). Thus far, ADHD is the pediatric disorder with some evidence for bupropion's efficacy (see below). This may in part be due to the fact that bupropion is structurally related to amphetamine and the sympathomimetic diethylpropion. It has few anticholinergic effects and does not alter cardiac conduction or cause orthostasis.

Chemical Properties

Bupropion is rapidly absorbed from the gastrointestinal (GI) tract after oral administration. It is primarily metabolized by the liver, and its metabolites hydroxybupropion and threohydrobupropion are excreted in the urine (AHFS, 2000). These metabolites may have particular clinical relevance. Golden and associates found that plasma hydroxybupropion concentrations greater than 1250 ng/mL were correlated with a lack of positive clinical response to bupropion therapy (Golden et al., 1988). Peak plasma concentrations are achieved within 2 hours (AHFS, 2000). The half-life of bupropion ranges from 8 to 24 hours (AHFS, 2000).

Indications

Attention-Deficit Hyperactivity Disorder

The use of bupropion as a potential second-line treatment for attention-deficit hyperactivity disorder (ADHD) has been substantiated by two open (Simeon et al., 1986; Riggs et al., 1998) and three controlled studies (Clay et al., 1988; Barrickman et al., 1995; Conners et al., 1996). Simeon and colleagues (1986) treated 17 male patients ranging in age from 7 to 13 years with ADHD and/or conduct disorders in an open clinical trial with a baseline placebo period of 4 weeks, 8 weeks of bupropion therapy, and 2 weeks of a postdrug placebo period (Simeon et al., 1986). Evaluations included clinical assessments, parents, teachers, and self-ratings, cognitive tests, and blood level measurements of bupropion. Fifteen patients received a daily maximum dose of 150 mg, one received 100 mg and one 50 mg. Clinical global improvement with bupropion therapy was marked in 5 patients, moderate in 7, mild in 2, and no improvement was observed in 3 patients. The authors did note that overall bupropion appeared to be less effective in improving core symptoms of ADHD such as poor attention span, distractibility, and impulsivity, although half of their patients were nonresponders to previous therapy (Simeon et al., 1986).

Clay and colleagues (1988) used bupropion to treat 30 prepubertal children with diagnoses of ADHD in a double-blind placebo-controlled study. Similar to Simeon and associates (1986), the authors found that children with prominent conduct disorder symptoms, or prior stimulant-resistant patients, responded well to bupropion. Optimal doses ranged from 3 to 7 mg/kg/day (100–250 mg/day). Some patients who did not respond well to bupropion responded well to methylphenidate prescribed openly at a later time (Clay et al., 1988).

Casat and colleagues (1989) also administered bupropion to 20 children with ADHD and placebo to 10 children with ADHD. Significant improvement was observed in the bupropion-treated group.

Finally, Conners and collaborators (1996) conducted a multisite, double-blind, placebo-controlled trial of bupropion for the treatment of children with ADHD. Seventy-two children with ADHD (6–12 years old) were randomized to receive bupropion (3–6 mg/kg/day) or placebo ($n = 37$), administered at 7 a.m. and 7 p.m. A significant treatment effect was apparent at day 3 for hyperactivity and conduct dysregulation on the Conners teacher's checklist, and at day 28 for conduct problems and impulsive behavior on the Conners Parent and Teacher Questionnaire. Four children had rash and urticaria requiring discontinuation of the drug (Conners et al., 1996).

Major Depressive Disorder

In adults, bupropion has been found to be as effective as standard antidepressant therapies in the treatment of MDD (Preskorn, 1983; Kavoussi et al., 1997). There are no controlled data in children and adolescents (McConville et al., 1998). Based on its preliminary success in treating some patients with ADHD, investigation into its role in the treatment of child and adolescent MDD is warranted. (See below regarding guidelines to minimize risk for seizures.)

Contraindications

Contraindications include the following:

- History of hypersensitivity reaction to bupropion.

- Pregnancy: bupropion crosses the placenta and is secreted in breast milk.

- A diagnosis of bulimia or anorexia nervosa: a higher incidence of seizures has been reported when bupropion is administered to these patients (Pope and Hudson, 1986).

- Bupropion should not be prescribed to patients on MAOIs. The patient should be off the MAOI for at least 2 weeks prior to the initiation of bupropion therapy.

Seizure Disorder–Related Precautions

Seizure is the side effect of most concern with bupropion (Storrow, 1994). Seizures have been found to occur in 0.4% of all patients treated with bupropion doses of 450 mg/day or less—a fourfold increased incidence compared to other antidepressants (AHFS, 2000). Moreover, the incidence of seizures increases at higher doses of bupropion so that at doses of 450–600 mg/day the risk is approximately 4% (AHFS, 2000). Because of this increased risk, it is recommended that daily doses of bupropion not exceed 450 mg. In addition, no individual dose

should be greater than 150 mg or be given more frequently than every 6 hours (AHFS, 2000).

Because of its significantly increased association with seizures (Tilton, 1998; AHFS, 2000), we do not recommend using bupropion in children and adolescents with a history of seizures, head trauma, central nervous system (CNS) tumor, or other organic brain disease. Although children and adolescents appear to be far less susceptible to severe withdrawal phenomena, including seizures, when alcohol and benzodiazepines are abruptly withdrawn (see Chapter 19), we do not recommend bupropion in such patients because of its increased association with seizures. Concomitant ingestion of other psychotropics such as haloperidol and lithium that may affect the seizure level is a relative contraindication to prescribing bupropion.

Other Side Effects

Agitation, restlessness, irritability (Golden et al., 1988), headache, insomnia, tremor, constipation, and nausea (Lineberry et al., 1990) may be common side effects seen with bupropion therapy (Physicians' Desk Reference, 2001). Weight loss may occur in approximately 25% of patients (Lineberry et al., 1990). Bupropion should be given cautiously to patients with liver or kidney disease. Bupropion is significantly safer than the TCAs when taken in overdose. Overdoses of bupropion when taken alone have not been fatal (AHFS, 2000).

Cognitive Effects

Clay and colleagues (1988) noted in their study in children with ADHD that bupropion had positive effects on memory performance, which may be unique among the antidepressants. Other antidepressants either have no effect or a negative effect on memory performance. It should be noted, however, that Ferguson and Simeon observed no adverse or positive effects on cognition on a cognitive battery in 17 children with ADHD or conduct disorders receiving bupropion (Ferguson and Simeon, 1984).

Dosage and Administration

Bupropion hydrochloride is available in 75 and 100 mg tablets (Wellbutrin® Glaxo Wellcome); and in 100 and 150 mg extended-release tablets (Wellbutrin® SR; Glaxo Wellcome) (AHFS, 2000). The drug usually is administered 3 times daily, with 6 or more hours separating doses (AHFS, 2000). As extended-release tablets, bupropion is administered twice daily in the morning and (noon) (or) evening (AHFS, 2000). Avoiding bedtime administration of the evening dose may lessen the occurrence of insomnia (AHFS, 2000). Because the sustained release preparation of bupropion has a reduced risk of side effects and may be

better tolerated, we recommend initiating treatment with sustained release bupropion rather than immediate release bupropion.

Prior to initiating a bupropion trial, children and adolescents should have a physical and neurological examination. A baseline screen for abnormal involuntary movements, including tics, should be performed. It is important to elicit any family history of motor movement tic disorders. Bupropion does cross the placenta so that a pregnancy test and evaluation for adequate contraceptive use is recommended in all females of child-bearing age since bupropion should not be prescribed during pregnancy. A thorough drug and alcohol evaluation should be conducted, since bupropion should not be started after recent withdrawal from alcohol or benzodiazepines. Use of drugs and alcohol while on bupropion should be discouraged. It is also important to determine the eating habits of patients being considered for bupropion therapy, since bupropion is contraindicated in patients with a current or past history of bulimia or anorexia nervosa (AHFS, 2000).

We recommend a baseline laboratory screen to include electrolytes (these may be abnormal in patients with bulimia or anorexia), liver and renal function tests, i.e., BUN/creatinine, to assess liver and kidney status, and urine drug screen. We also recommend obtaining a baseline EEG to rule out underlying EEG irregularities. Although bupropion is not believed to cause cardiac side effects (AHFS, 2000), the lack of data in pediatric patients with cardiac disease supports obtaining vital signs (e.g., pulse and blood pressure) and a baseline EKG prior to starting bupropion therapy. When children and adolescents are treated with bupropion, they should be monitored at each visit for any involuntary movements/tics by observation and history. Whenever the dose is increased, it is important to check blood pressure, pulse, height, and weight. In addition, it is advisable to record height and weight at regular 3- to 4-month intervals. Plasma concentrations of bupropion have not been found to be helpful in titration of medication, although in adults one study found that plasma hydroxybupropion concentrations above 1.250 ng/mL were associated with a lack of clinical response (Golden et al., 1988). Therefore, if access to a laboratory that analyzes bupropion's metabolites is available, ordering these plasma concentrations may be useful.

Drug Interactions

Caution should be observed with concurrent administration of bupropion and drugs (e.g., antidepressants, antipsychotics, theophylline, corticosteroids) that lower the seizure threshold (AHFS, 2000). Therapy should be initiated with low doses, and dosage should be increased gradually (AHFS, 2000). Cytochrome P-450 isoenzyme (e.g., CYP2D6) interactions also necessitate caution when bupropion is administered concomitantly with drugs that may induce (e.g., carbamazepine) or inhibit its metabolism (e.g., cimetidine), since bupropion is metabo-

lized to hydroxybupropion (morpholinol) via this isoenzyme system (AHFS, 2000).

NEFAZODONE

Nefazodone (NFZ) is a phenylpiperazine-derivative antidepressant agent (Fontaine, 1993). It differs pharmacologically from SSRIs and TCAs (Mayol et al., 1994). Nefazodone's mechanisms of action involve inhibition of reuptake of 5-HT at the presynaptic membrane and antagonism at serotonin type 2 (5-HT₂) receptors (Ansseau et al., 1994). Nefazodone also inhibits presynaptic reuptake of norepinephrine (NE) and exhibits α_1 -adrenergic blocking activity (Fontaine, 1993). Double-blind controlled trials have shown that nefazodone at doses of 300–400 mg/day is superior to placebo and equivalent in efficacy to imipramine and fluoxetine (Preskorn and Burke, 1992). Dosage exceeding 500 mg/day may not have an advantage over placebo (Preskorn and Burke, 1992).

Pharmacokinetics

Nefazodone is rapidly absorbed, has a short half-life of 2–4 hours, and has multiple active metabolites (Findling et al., 2000). The half-life of nefazodone and two of its metabolites [hydroxynefazodone (OH-NF) and meta-chlorphenylpiperazine (mCPP)] appears shorter in children and adolescents compared to adults (Findling et al., 2000). It undergoes hepatic metabolism, mostly through the p450 IIIA4 isoenzyme system (Nemeroff, 1994).

Indications

The efficacy of nefazodone for the treatment of MDD in adults has been established by controlled studies in outpatient settings (Rickels et al., 1994). The safety and efficacy of nefazodone in pediatric populations has been evaluated in a case series by Wilens et al. (1997) and by an open-label study of the pharmacokinetics of nefazodone in children (Findling et al., 2000).

Wilens et al. (1997) treated 7 treatment-refractory children and adolescents (mean age 12.4) with juvenile mood disorder with nefazodone at a mean daily dose of 357 mg (3.4 mg/kg) for 13 (+/–8) weeks. Of the seven children, three had MDD, two had dysthymia, and four had bipolar disorder. Overall concurrent medications included lithium, clonazepam, valproic acid, paroxetine, clonidine, guanfacine, and methylphenidate (Wilens et al., 1997). Nefazodone was started at 50 mg daily and titrated upward at 3- to 7- day intervals in twice-a-day dosing (Wilens et al., 1997). Four (56%) patients had much (42%) to very much (14%) clinical improvement in depression. Two of the children with bipolar disorder had mild manic activation, a percentage considered acceptable by the authors due to a prior history of manic activation for these patients on other standard

antidepressants (Wilens et al., 1997). In agreement with Wilens and colleagues, one would expect a more robust antidepressant response in treatment-naive patients (1997).

In the Findling study (2000), 15 depressed children (mean age 10) and 13 depressed adolescents (mean age 14) received an 8-week open-label trial of nefazodone with blood sampling over three separate 12-hour periods for pharmacokinetic analyses of nefazodone and three of its active metabolites. Treatment was started at a dose of 50 mg twice daily, titrated up to 100 mg twice daily, on the ninth day and thereafter for 6 more weeks to maximize clinical response for 6 more weeks (Findling et al., 2000). Children received a maximum daily dose of 150 mg bid, and adolescents a maximum daily dose of 300 mg bid. Plasma nefazodone concentrations were higher in children compared to adolescents. Using the a priori criteria for response (CGI improvement score at the end of the study of “much” or “very much” improved), 86% of children and 69% of adolescents were considered responders, a result associated with significant reductions in depressive symptoms. At the end of week 8, the average daily nefazodone dose was 233 mg for children and 342 mg for adolescents (Findling et al., 2000). Compared to published data in adults, the half-life of NFZ and two of its metabolites appeared shorter in children and adolescents. Nefazodone was overall well tolerated, even in patients who were poor metabolizers (Findling et al., 2000). The most common reported side effects were headache, nausea, vomiting, and anorexia.

Dosage and Administration

Nefazodone comes in 50, 100, 150, 200, and 250 mg oral tablets (Serzone[®], Bristol-Myers Squibb). The effective dosage of nefazodone in the pediatric clinical studies has ranged from a maximum daily dose of 150 mg bid for children to 300 mg bid for adolescents daily (Findling et al., 2000). In the Wilens et al. study (1997), the mean daily dose was 357 mg. Therapy with nefazodone should be initiated at a dosage of 25–50 mg twice daily (morning and evening) and titrated to an effective dose by 50 mg weekly (Findling et al., 2000). Nefazodone is usually administered in two divided doses daily (AHFS, 2000), but could also be administered three or four times daily due to its short half-life.

Side Effects

Commonly cited dose-dependent, treatment-emergent adverse effects for nefazodone are nausea, dizziness, and somnolence (AHFS, 2000). In a recent comparative analysis with a number of other antidepressants (e.g., paroxetine, fluoxetine, venlafaxine, imipramine), dizziness was most common with nefazodone (Preskorn et al., 1994). The mechanism for the dizziness is likely to be in part due to

α_1 receptor antagonism nefazodone but may also be related to 5-HT-2A receptor antagonism also.

Concomitant administration with food delays absorption and may decrease bioavailability of nefazodone by about 20% (AHFS, 2000). Coadministration of nefazodone and triazolam may cause a significant increase in plasma concentrations of triazolam and generally should be avoided (AHFS, 2000). A drug-free interval of at least 2 weeks should elapse when switching a patient from an MAOI to nefazodone (AHFS, 2000).

Nefazodone's potential drug interactions/contraindications (AHFS, 2000) are as follows:

Nefazodone/Pimozide

Nefazodone/Fluvoxamine/Cisapride

Nefazodone /MAOIs/Furazolidone

Nefazodone /Nonsedating Antihistamines/ Sibutramine

MIRTAZAPINE

Mirtazapine is a piperazinoazepine-derivative antidepressant agent (AHFS, 2000). It differs structurally from SSRIs and TCAs (AHFS, 2000). Mirtazapine appears to act as an antagonist of the central presynaptic α_2 -adrenergic autoreceptors and heteroreceptors, resulting in an antidepressant effect related to enhanced central noradrenergic and serotonergic activity (Gorman, 1999). It is also an antagonist of 5-HT₂ and 5-HT₃ receptors and an enhancer of 5-HT_{1A}-mediated neurotransmission (Gorman, 1999). Mirtazapine antagonizes histamine H₁ receptors, which may account for its sedative effects (AHFS, 2000), especially in the low-dosage range. In addition, mirtazapine exhibits moderate peripheral α_1 -adrenergic blockade, reportedly causing occasional orthostatic hypotension (AHFS, 2000).

Indications

Major Depressive Disorder

Mirtazapine is FDA approved for the treatment of MDD in adults (Montgomery et al., 1998). Its antidepressant efficacy has been established by controlled studies (Stahl et al., 1997; Fawcett and Barkin, 1998) showing an effect greater than placebo but comparable to TCAs (Montgomery et al., 1998), and fluoxetine (Wheatley et al., 1998). Its noradrenergic and serotonergic enhancement has suggested an earlier onset of action than SSRIs (Rosenbaum and Nierenberg, 1999), although a faster drop in antidepressant rating scores may be secondary to its antihistamine-mediated sedation (Preskorn and Irwin, 1982). The antidepressant efficacy of mirtazapine in children and younger adolescents has not been estab-

lished (AHFS, 2000). Its use in children is considered empiric at this time, until data on safety and efficacy are available.

Posttraumatic Stress Disorder

An open-label study of mirtazapine for the treatment of pediatric posttraumatic stress disorder (PTSD) was recently conducted by Connor and collaborators (1999). Using up to 45 mg/day for 8 weeks, the authors reported improvement (>50%) in 50% of the sample comparing baseline with global ratings at weeks 2, 4, 6, and 8. Improvements in self-rated scales of depression were also noted. The drug was well tolerated with few significant side effects (Connor et al., 1999). This is an interesting pilot study, which deserves controlled replication.

Insomnia

A recent polysomnographic study looking at the effect of mirtazapine on sleep architecture at baseline and after 1 week (on 15 mg at bedtime) and 2 weeks (30 mg at bedtime) reported significantly decreased sleep latency, and significantly increased total sleep time after 1 week in 6 adults (and adolescents) with MDD (Winokur et al., 2000). Results of this study could theoretically support the judicious use of this compound in children and adolescents suffering from rebound hyperactivity at bedtime or insomnia secondary to a mood disorder.

Dosage and Administration

Mirtazapine is available in 15, 30, and 45 mg tablets (Remeron[®]; Organon) (AHFS, 2000). It can be administered once daily, with meals, usually at bedtime (AHFS, 2000). The recommended initial dosage in adults is 15 mg daily. Dosage may be increased up to a maximum of 45 mg daily (Wheatley et al., 1998) at intervals of 1–2 weeks (AHFS, 2000). Its elimination half-life in adults is 20–40 hours (AHFS, 2000). Mirtazapine does not have FDA approval for use in children and adolescents. The effective dosage of mirtazapine for the treatment of pediatric MDD is not known.

Side Effects

One of the most common adverse effects of mirtazapine is sedation (Puzantian, 1998). Weight gain, also mediated by the antihistamine mechanism, has been anecdotally reported as a worrisome potential side effect of mirtazapine (AHFS, 2000).

A recent double-blind study compared a fixed regimen of 30 mg of mirtazapine at bedtime with one increase in dose from 15 to 30 mg at bedtime after the first week for 2 weeks in adult patients with MDD (Radhakishun et al., 2000). Using an interactive telephone system and estimated sleep recordings on self-rating scales, daytime alertness ratings for both dosages were considered subnor-

mal at baseline, but equally improved for both groups thereafter through week 2 of the study. Both groups reported sleeping an average of 6–6.2 hours/night at baseline and 7.4–7.9 hours/night after starting medication. The average sleep duration was significantly higher for the fixed-dose group compared to the ascending-dose group. Daytime somnolence, nevertheless, was reported by 7–10% of both groups during both weeks of treatment. The investigator's conclusion that mirtazapine facilitated sleep without reducing daytime alertness is somewhat offset by this finding (Radhakishun et al., 2000). This study does not assist the child psychiatrist with the clinical decision of whether 7.5 or 15 mg of mirtazapine is the most adequate pediatric dose for empiric treatment of insomnia. It documents that both 15 and 30 mg of mirtazapine could have a hypnotic effect in adults with MDD.

Since hypomanic episodes have been reported in patients receiving mirtazapine, the drug should be used with caution in patients with a history of hypomanic or manic attacks (AHFS, 2000). Mirtazapine has low affinity for muscarinic cholinergic receptors and α_1 -adrenergic receptors and therefore produces minimal anticholinergic side effects or orthostatic hypotension (Preskorn and Burke, 1992). Minimal induced anxiety reported in adults seems to be consistent with the drug's antagonism of 5-HT-2C receptors (Sussman, 1994).

Mirtazapine's potential drug interactions/contraindications (AHFS, 2000) are as follows:

- TCAs/Mirtazapine
- MAOIs/Mirtazapine
- Furazolidone/Mirtazapine

VENLAFAXINE

Venlafaxine is a phenylethylamine-derivative antidepressant agent, structurally unrelated to other currently available antidepressants (AHFS, 2000). Venlafaxine inhibits 5-HT uptake at low doses and inhibits the neuronal reuptake of 5HT and NE at high doses (Harvey et al., 2000).

Indications

Venlafaxine has FDA approval for the treatment of adults with MDD (AHFS, 2000). Controlled studies in adult outpatient and inpatient settings have demonstrated venlafaxine's antidepressant efficacy (on mean dosages of 375 mg/day) over placebo (Preskorn and Burke, 1992). Inhibition of both 5-HT and NE reuptake may produce a more rapid development of β -adrenergic receptor downregulation than SSRIs (Baron et al., 1988). Its use in children and adolescents has been limited. At the time of this writing, only one controlled study of venlafaxine

in children and adolescents has been published (Mandoki et al., 1997), and data are not yet available for recently completed studies.

In a double-blind, placebo-controlled, 6-week study, Mandoki et al. (1997) compared venlafaxine plus the addition of therapy or placebo for the treatment of depression in 33 subjects between the ages of 8 and 17. No significant therapeutic differences were found between the two groups as measured by weekly rating assessments, despite improvement shown by both groups over time. Venlafaxine was overall well tolerated. The low dosage used (37.5 mg/day for children; 75 mg/day for adolescents), the lack of baseline observation, and short duration of the trial may account for the negative findings.

In a 5-week open trial of venlafaxine (mean daily dose of 60 mg) conducted in 14 children and adolescents (mean age 11.6 years) with ADHD, 7 subjects had a decrease of at least one standard deviation from their baseline on a standard rating scale (Olvera et al., 1996). There were no statistically significant effects of venlafaxine on reaction times or on the number of commission and omission errors on a computerized test of attention (Olvera et al., 1996). Three subjects displayed a worsening of hyperactivity and required discontinuation of the drug. No effects on blood pressure or heart rate were noticed. Despite overall improvement in ADHD symptoms, this study suggests that venlafaxine may aggravate hyperactivity (Olvera et al., 1996), requiring cautious use of this drug in children with ADHD.

Data are not yet available for a double-blind, placebo-controlled study completed by Wyeth Ayerst on venlafaxine in children and adolescents with MDD, nor for an ongoing double-blind placebo-controlled study of venlafaxine in adolescents (12–17 years) with social anxiety disorder (social phobia). The FDA has recently initiated a follow-up study of venlafaxine in pediatric patients with MDD (7–17 years) and also recently initiated a 6-month, long-term, open-label safety study of venlafaxine XR in pediatric MDD patients.

In summary, since the efficacy of venlafaxine has not been established for the treatment of childhood disorders, there is a need for controlled studies on both MDD and childhood ADHD.

Dosage and Administration

Venlafaxine is available in 25, 37.5, 50, and 100 mg tablets (Effexor®; Wyeth-Ayerst) and as 37.5, 75, and 150 mg extended-release capsules, (Effexor® XR; Wyeth-Ayerst). The recommended initial dosage of venlafaxine in adults is 37.5–75 mg daily administered in two or three divided doses or as a single daily dose when using the extended-release capsules (AHFS, 2000). Pediatric FDA dosage guidelines are not available. An initial dose of 37.5 mg daily (in 2 divided doses) for the first 7 days followed by an increase to 75 mg daily may be considered

for pediatric patients (AHFS, 2000). Dosages should be increased with caution in this population. In adults the dosage is increased by increments of 75 mg daily at intervals of not less than 4 days up to 225–350 mg daily in divided doses (Janicak et al., 2001), although outpatient studies have not demonstrate additional benefit from dosages exceeding 225 mg (Preskorn et al., 1994). The manufacturer recommends that if venlafaxine therapy is to be discontinued, the dosage should be decreased gradually to reduce the risk of withdrawal symptoms (i.e., dizziness, headache, gastrointestinal discomfort) (AHFS, 2000).

Side Effects

Except for the potential increase in blood pressure, venlafaxine appears to have a side effect profile similar to the SSRIs (Preskorn and Burke, 1992). Dizziness, nervousness, tremor, sedation, and sweating have been described as dose-dependent side effects (Preskorn and Burke, 1992). The described increase in blood pressure (rare below doses of 225 mg/day) is probably related to venlafaxine's potentiation of NE reuptake inhibition (Preskorn and Burke, 1992). Venlafaxine (like nefazodone and mirtazapine) has no direct effects on cardiac conduction (AHFS, 2000). There seems to be anecdotal agreement among practitioners treating adults and children that problematic side effects may dissipate on venlafaxine XR.

THYROID HORMONES

The use of thyroid hormones in psychiatry is based on models similar to the augmentation of antidepressant therapy with lithium (Kaplan and Sadock, 1991). L-Triiodothyronine (T3 or L-triiodothyronine; Cytomel™), the most commonly used thyroid hormone, is used as an adjuvant to an antidepressant medication in an attempt to convert patient nonresponders or partial responders (Kaplan and Sadock, 1991). More rarely, thyroxin (T4 or levothyroxine; Levoxine™, Levothroid™, and Synthroid™) is sometimes used for the same purpose. Endogenous and exogenous T4 is converted in the body into triiodothyronine (Kaplan and Sadock, 1991).

Chemical Properties

Thyroid hormones undergo variable absorption by the GI tract after oral absorption (Kaplan & Sadock, 1991). Absorption can be decreased by food and is increased when administered on an empty stomach. The half-life of T3 is 1–2 days, while the half-life of T4 is 6–7 days. The mechanism of action for thyroid hormone increase of antidepressant effectiveness is unknown.

Indications

Thyroid hormone treatment may be used in psychiatry as an adjuvant to antidepressants. T3 or T4 supplementation, like lithium augmentation of antidepressant therapy, is indicated if an adult patient has been nonresponsive or only partially responsive to a 6-week course of antidepressant therapy at appropriate doses. (For information on lithium augmentation see Chapter 13.) T3 is believed to be more effective than T4. In standard clinical practice, lithium is generally added to an antidepressant regimen before T3 augmentation is instituted. Several controlled studies have indicated that T3 converts 33–75% of antidepressant responders, while several other studies have failed to find such a relationship (Kaplan and Sadock, 1991). There are no comparable data in children and adolescents.

Contraindications

Thyroid hormones should not be given to patients with cardiac disease or hypertension (Kaplan and Sadock, 1991). Thyroid hormones may increase the insulin requirements of diabetic patients (Kaplan and Sadock, 1991). Thus, diabetes is a relative contraindication to the administration of thyroid hormones.

Side Effects

Weight loss, palpitations, nervousness, diarrhea, abdominal cramps, sweating, tachycardia, increased blood pressure, tremors, headache, and insomnia are the reported side effects of thyroid hormone therapy (Kaplan and Sadock, 1991). Overdoses can lead to cardiac failure and death (Kaplan and Sadock, 1991). Immediate emergency and intensive care unit (ICU) monitoring are required.

Dosage and Administration

In adults who have failed to respond to antidepressants after 6 weeks of therapy, 25–50 µg/day of T3 may be added to the patient's regimen (Kaplan and Sadock, 1991). T3 can be used as an adjunct for all of the TCAs and trazodone in adults. There is very limited data on its use with bupropion or fluoxetine and no information on its use with sertraline. An adequate trial of T3 supplementation is 7–14 days (Kaplan and Sadock, 1991). If it is successful, it should be continued for 2 months, and then tapered at the rate of 12.5 µg per day every 3–7 days. There are no comparable data in children and adolescents. Until safety and efficacy data in children and adolescents with psychiatric illness become available, we only hesitantly recommend its use in selected cases.

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Monoamine Oxidase Inhibitors

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Monoamine oxidase inhibitors (MAOIs) are a class of antidepressant defined by function rather than structure. All drugs in this class either reversibly or irreversibly inhibit the enzyme monoamine oxidase (MAO). Although these agents have been the focus of intensive biochemical and clinical research over the past 50 years, their popularity in psychiatric practice has varied tremendously. By the late 1960s several indications had emerged, and new agents were available for the treatment of depression and anxiety disorders. Soon thereafter the prototype MAOI, iproniazid, was removed from the market when it was associated with hepatic failure (Goldberg, 1964). Phenelzine and tranylcypromine fell from favor when cases of hypertensive crisis were recognized and efficacy based on early trials was questioned (Youdim, 1975). Today, MAOIs have restricted applications in child psychiatry due to their potential adverse effects related to dietary noncompliance. *No MAOI compound is currently FDA approved for psychiatric indications in children under 16 years of age.*

MAOIs remain important investigative tools despite their decline in clinical use, perhaps due to the central role of MAO in neurophysiology (Youdim, 1975). The emergence of new and more stringently controlled clinical trials, the ability to manage hypertensive reactions through dietary restriction of tyramine, and the

synthesis of several new MAOIs that are less sensitive to tyramine has kept these agents at the forefront of clinical research (Samson et al., 1985).

MAOIs are not considered first-line therapy for any disorder, but are frequently the second or third choice of agents for the treatment of depressed adults with anxious or atypical symptoms (Paykel and White, 1989). Since tricyclic antidepressants (TCAs) are widely studied and have historically been viewed as lower risk, MAOI use in young people has been especially limited. Disorders that may potentially respond to MAOIs in children and adolescents include atypical depression, treatment-resistant depression, bulimia, panic disorder, and social phobia. MAOI therapy represents a target for future research in child and adolescent psychiatry, especially with the promise of reversible inhibitors of MAO-A being eventually introduced in the United States.

CHEMICAL PROPERTIES

The discovery that monoamine oxidase inhibitors “elevate” mood predates the same discovery for tricyclic compounds, making MAOIs the oldest class of antidepressant in current use. Iproniazid was noted to cause euphoria during investigational use for tuberculosis in the early 1950s, an effect that was not shared by the related (weak MAOI) compound isoniazid (Bloch et al., 1954). Several successful reports of iproniazid in the treatment of depression followed (Loomer et al., 1958; West and Dally, 1959). Since that time, three MAOI compounds have been marketed in the United States for psychiatric indications: phenelzine (Nardil™), tranylcypromine (Parnate™), and isocarboxazid (Marplan™) (Fig. 1). Two other compounds, furazolidone (Furoxone™) and procarbazine (Matulane™), are marketed as antimicrobial and antineoplastic agents, respectively. However, several others are in use internationally or under investigation (Table 1). MAOIs have been chemically classified as hydrazine (isocarboxazid, phenelzine) and nonhydrazine agents (tranylcypromine), although many compounds under current investigation are structurally unique.

Absorption and Metabolism

Peak levels of both phenelzine and tranylcypromine are reached within 2 hours after a single oral dose. Maximum enzyme inhibition is achieved after 7–14 days of chronic administration (Murphy et al., 1977). The elimination half-lives of phenelzine and tranylcypromine are less than 3 hours (Amrein et al., 1989). However, since both are irreversible inhibitors, once the drug binds to MAO the enzyme is effectively removed from the system. The resulting reduction in MAO activity persists as long as 2 weeks after the drug has been metabolized, while new enzyme is synthesized (Murphy et al., 1977; McDaniel, 1986; Larsen, 1988). Amrein and colleagues (1989) have demonstrated the pharmacodynamic distinc-

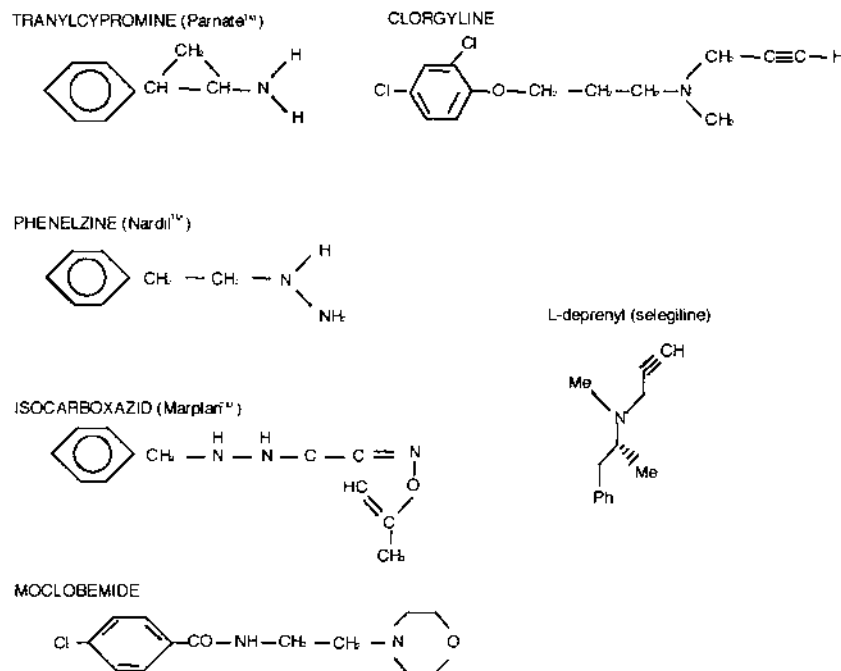


FIGURE 1 Chemical structures of some MAOI drugs.

tion between reversible and irreversible MAOIs by comparing the activities of tranylcypromine (irreversible, nonspecific) and moclobemide (reversible MAOI-A). Both are eliminated quickly, with half-lives of approximately 2 hours, but MAO activity returns to normal 24 hours after discontinuation of moclobemide. The elimination half-lives of reversible MAOIs vary to a greater degree than currently approved agents and may be as long as 12–15 hours (Amrein et al., 1989).

Acetylation Rate

The metabolism rates of some MAOIs are influenced by acetylation phenotype. In the late 1950s it was recognized that the rate of isoniazid metabolism showed a bimodal population distribution (Evans et al., 1960). Slow or fast metabolism proved to be genetically characterized by activity of the hepatic enzyme acetyltransferase. Phenelzine metabolism is particularly dependent on acetylation trait, and some, but not all (Rose, 1982), early studies found that individuals with the slow acetylation trait showed superior clinical response and increased side effects

TABLE 1 FDA Approval and Indications for Monoamine Oxidase Inhibitors

MAO Inhibitor	Kinetics	FDA Approval	Indications
Nonselective			
Iproniazid (Marsalid [®])	IRR	Withdrawn	Antidepressant
Isocarboxazid (Marplan [®])	IRR	Probable (≥ 16 yr)	Refractory depression
Phenelzine (Nardil [®])	IRR	APP (≥ 16 yr)	Atypical depression
Tranylcypromine (Parnate [®])	IRR ^a	APP (adult)	Major depression w/o melancholia
Selective MAO-A			
Clorgyline	IRR ^b	NA	Similar to nonselective MAOIs
Moclobemide	REV	NA	Probably for depressive disorders
Selective MAO-B			
L-Deprenyl (selegiline)	IRR ^b	NA	Possible use in Parkinson's disease
Pargyline (Eutonyl [®])	IRR ^b	Withdrawn	Antihypertensive
Uncharacterized			
Furazolidone (Furoxone [®])	?	APP (≥ 1 month)	Antimicrobial
Procarbazine (Matulane [®])	?	APP (any age)	Stage III–IV Hodgkin's disease

^a Partially reversible in vitro.

^b Nonselective at higher doses.

NA = Not approved in the United States; APP = approved (age range); IRR = irreversible MAOI; REV = reversible competitive MAOI. Source: Raskin, 1972; Mountjoy et al., 1980; Dingemans et al., 1995.

with phenelzine (Paykel et al., 1982). In bipolar depression, clinical response correlates with peak plasma levels of tranylcypromine, but not with the rate of elimination (Mallinger et al., 1990). No study has examined the predictive value of acetylation trait when platelet MAO inhibition is controlled at >80%. Preliminary experience with moclobemide suggests that its metabolism is not greatly influenced by acetylation phenotype (Schoerlin et al., 1971).

Mechanism of Action

The common site of action for MAOIs is the ubiquitous mitochondrial enzyme monoamine oxidase. This enzyme deaminates a variety of substrates including serotonin, epinephrine, norepinephrine, tyramine, and dopamine. MAO exists in at least two isoenzyme forms, A and B, which differ in substrate preference, systemic distribution, and sensitivity to specific MAOIs. Both are present in the central nervous system (CNS). Although both forms metabolize tyramine and dopamine, MAO-A (present in norepinephrine and dopamine neurons) preferentially deaminates norepinephrine and serotonin. MAO-B (present to a large extent in serotonin-containing neurons) preferentially deaminates tyramine and accounts for the majority of dopamine metabolism in the striatum. Of note, the preferential substrates do not correspond to the preferential localizations in the CNS. Cortical dopamine is primarily metabolized by MAO-A (Af Klinteberg et al., 1987b; Mann et al., 1989).

The three agents commonly prescribed in the United States are nonselective, inhibiting both forms of the enzyme. However, experimental use of selective inhibitors such as moclobemide, clorgyline (MAOI-A), and L-deprenyl (selegiline, MAOI-B) has revealed functional differences between MAO subtypes. Selective MAO-B inhibitors are less effective in depression and are not sensitive to dietary tyramine. Therefore, the antidepressant and pressor effects of MAOIs (Pickar et al., 1981) are mediated by MAO-A inhibition, as demonstrated by Mann and associates (1989) in a controlled trial of L-deprenyl. At low doses L-deprenyl is a selective MAO-B inhibitor and shows no greater antidepressant effect than placebo. At higher doses the drug is less selective, inhibiting both MAO-A and MAO-B, and does show significant antidepressant properties (Mann et al., 1989).

As with all antidepressants, the precise mechanism of action of MAOIs is limited by our understanding of the pathophysiology of affective disorders. In its simplest form, the "amine hypothesis" attributes depressive symptoms to underactivity of serotonin and/or norepinephrine, which may be treated either by blocking reuptake of amine neurotransmitters (via TCAs) or by slowing their metabolism (via MAOIs) (Baldessarini, 1975). Yet both tricyclic compounds and MAOIs require 2–4 weeks of administration before producing clinical benefit, despite immediate neurotransmitter changes. MAOI administration initially in-

creases intracellular levels of both CNS and peripheral substrates. MAO-A inhibitors cause a rise in serotonin and norepinephrine levels preferentially, while MAO-B inhibitors have a greater effect on systemic dopamine levels (Larsen, 1988). Chronic administration is associated with return of these neurotransmitters levels to baseline but long-term changes in receptor populations (McDaniel et al., 1986). It is this latter change in receptor density that is thought to mediate the clinical effects of MAOIs. Interestingly, tricyclic antidepressants have also been shown to weakly inhibit MAO, suggesting that MAO inhibition may represent a common therapeutic mechanism for both categories of drug (Sullivan et al., 1977).

Platelet MAO Assays

Some data suggest that a threshold level of MAO inhibition is required for these drugs to be effective for depression, as measured by percent inhibition of platelet MAO. Correlations with symptom response suggest a clinical threshold at 80–90% platelet enzyme inhibition (Raft et al., 1981). This threshold is further supported by Ravaris and colleagues' (1976) demonstration that phenelzine was not superior to placebo at 60% inhibition, but was superior to placebo at a mean platelet MAO inhibition of 83% (Ravaris et al., 1976). The use of platelet MAO activity to assess adequate central MAO inhibition is not applicable to newer, selective MAO-A inhibitors, since platelet MAO is type B (Wiesel et al., 1985).

MOCLOBEMIDE

Moclobemide is a reversible inhibitor of MAO-A enzyme, currently not available in the United States. Although it increases the concentration of dopamine, norepinephrine, and serotonin (i.e., in rat brain), the recovery of MAO-A activity is much quicker than with other MAOIs (Krishnan, 1998). This property accounts for the drug's partial potentiation of tyramine's blood pressor effect (Krishnan, 1998) and potential lack of interaction with amitriptyline or clomipramine (Dingemans et al., 1995).

Peak plasma concentrations are reached in 1 hour after oral administration, and the half-life of the compound is approximately 12 hours. Moclobemide can affect the pharmacokinetics of drugs that are mainly metabolized by cytochrome enzyme P4502D6 (CYP2D6), acting as an inhibitor of this system (Hartter et al., 1998). Recent controlled trials of moclobemide for the treatment of panic disorder with agoraphobia (Loerch et al., 1999) and social phobia (Schneier et al., 1992) have shown lack of efficacy in samples including older adolescents. Conversely, controlled studies involving adolescents have demonstrated moclobemide's superiority over placebo for the treatment of depression (Versiani et al., 1997; Tanghe et al., 1997; Stahl et al., 1995; Silverstone, 1993) and dysthymia. Hebenstreit

and colleagues (1990) reported comparable efficacy of moclobemide (300–600 mg/d) with imipramine (100–200 mg/d) in subjects with major depression (by DSM III criteria). A recent double-blind, randomized, clinical trial comparing the efficacy and tolerability of moclobemide versus fluoxetine for the treatment of depression suggested that both agents have a similar efficacy and tolerability but that moclobemide may have an earlier onset of antidepressive action (Gattaz et al., 1995). Dry mouth and tachycardia have been described with the use of moclobemide in adults and adolescents with depression (Tanghe et al., 1997).

MAOI INDICATIONS

General Issues in Children and Adolescents

Safety and efficacy of isocarboxazid (Marplan™) or phenelzine (Nardil™) in children younger than 16 years of age have not been established (AHFS, 2000). Tranylcypromine (Parnate™) has been approved only for adults (AHFS, 2000). In pediatric populations, adult guidelines for depressive, anxiety, and eating disorders may be applied, with additional care afforded due to issues of compliance and dietary restrictions (Ryan et al., 1988; Ryan, 1990). Preliminary studies of MAOIs for attention-deficit hyperactivity disorder (ADHD) are promising and may eventually lead to inclusion of these agents among accepted therapies for younger children. Since selective, reversible agents such as moclobemide may eventually become available in the United States, the risk factors that traditionally limited MAOIs prescription in younger children may become irrelevant. Therefore, child and adolescent psychiatrists should be familiar with most indications for MAOIs (Table 2), regardless of current approval.

Depressive Disorders

Subtypes of Depression

The primary indication for MAOIs is depression. Although there is evidence that these agents may be superior to TCAs in treating some subtypes of depression, the clinical distinction of subtypes remains difficult, especially in children and adolescents. The current diagnostic system in the United States, DSM-IV, organizes affective disorders into major categories distinguished by symptom criteria (Table 3) (American Psychiatric Association, 1994). Recognized subtypes of unipolar major depression include atypical, catatonic, psychotic, melancholic, and postpartum. Early drug trials may have compared “endogenous and reactive,” “primary and secondary,” or “psychotic, neurotic, and anxious” subtypes. Of these, endogenous depression most closely corresponds with DSM-IV criteria for major depressive disorder (American Psychiatric Association, 1994). The defini-

TABLE 2 Psychiatric Indications for Monoamine Oxidase Inhibitor Drugs

Approved	"Atypical" depression Major depression without melancholia ("nonendogenous") Depressive disorders refractory to TCAs
Probable	Major depression (all types) Panic disorder with or without agoraphobia Social phobia/agoraphobia without panic Borderline personality disorder with depression
Experimental	Attention-deficit hyperactivity disorder Childhood depression (<16 years) Anorexia and bulimia Borderline personality disorder without depression Separation anxiety/school phobia

tion of "melancholia," a current subtype of major depression, has remained fairly stable. However, other subtypes have been variably defined across research sites, producing heterogeneous samples in most early studies.

Atypical Depression

After MAOIs fell out of favor in the 1960s, one of the few persistent indications was "atypical depression" (West and Dally, 1959). After more than 30 years

TABLE 3 DSM-IV
 Diagnostic Categories for
 Depressive Illness and
 Subtypes

Major Depressive Disorder
with catatonic features
with melancholic features
with psychotic features
with atypical features
with postpartum onset
Dysthymia
early onset (before age 21)
late onset (age 21 or older)
with atypical features
Depressive Disorder, NOS

Source: American Hospital Formulary Service, 2000.

this term remains difficult to define. In the broadest sense, “atypical” refers to any depressive disorder, that does not exhibit classic signs of endogenous or melancholic depression. The original and most common definition of atypical depression is *a subtype of major depression* with “reversed” neurovegetative signs: weight gain rather than loss, hypersomnia rather than insomnia, mood reactivity, and mood worsening in the evening rather than morning (West and Dally, 1959). This subtype is not included in DSM-IV but is the only approved indication for MAOI therapy in adults (Parnate™) or adolescents older than 16 years of age (Nardil™; Marplan™).

Several early studies reported preferential response of atypical depression to MAOIs (West and Dally, 1959; Sargent, 1962). However, patient samples included subjects with prominent anxiety symptoms, a separate indication for MAOIs. These early trials are limited not only by heterogeneous patient samples, but also by simultaneous treatment with other medications and variable dosing strategies (Lesse, 1978; Mountjoy et al., 1980). Analysis of specific symptom response was often narrow, using global ratings of neurosis or anxiety. This liability was addressed in one early double-blind comparison of phenelzine to amitriptyline in 130 depressed outpatients. Ravaris and colleagues (1980) used structured interviews to rate improvement and derive a “Diagnostic Index” to distinguish endogenous from nonendogenous depression. The medications produced equal improvement on global scales with no difference between endogenous and nonendogenous classifications. However, mood reactivity, as an isolated symptom, responded significantly better to phenelzine, while sleep disturbance responded better to amitriptyline (Ravaris et al., 1976).

Later attempts to predict response to MAOIs were more discriminating in both symptom definition and patient selection. Parsons and colleagues (1989) studied a large number of subjects with atypical depression defined as “meeting DSM-III-R criteria for major depression or dysthymia who have reactive mood and any associated atypical symptoms (hyperphagia, hypersomnolence, rejection sensitivity, or leaden paralysis)” (Parsons et al., 1989). Forty-seven percent of these subjects also met criteria for borderline personality disorder (discussed below). In three reports of this large data set, they found that the number of atypical symptoms is a strong positive predictor of response to phenelzine and negative predictor of response to imipramine (Liebowitz et al., 1984, 1988; Parsons et al., 1989; Stewart et al., 1989). Similarly, Kayser and colleagues (1988) used structured symptom inventories to evaluate response to phenelzine and amitriptyline in 169 depressed outpatients. The results were analyzed both on the basis of depressive subtypes (melancholic and nonmelancholic major depression, minor depression, and atypical depression) and on the basis of symptom groups (depressive, somatic, anxiety, and interpersonal sensitivity). Atypical depression was defined as having mood reactivity plus two or more of the following: hypersomnia, hyperphagia or weight gain, leaden paralysis, and high interpersonal insensi-

tivity. In symptom-based analysis, phenelzine was superior to amitriptyline for phobic anxiety, general anxiety, and interpersonal sensitivity symptoms, accounting for a significant overall superiority of phenelzine after 6 weeks of therapy. However, response was statistically equivalent when patients were grouped by predefined subtypes, including atypical depression (Kayser et al., 1988). In contrast to the majority of studies, Davidson and associates (1991) did not find atypical symptoms to be significant positive predictors of MAOI response (Davidson et al., 1991). One possible explanation is that atypical symptoms predict a negative response to tricyclic agents, rather than a strong positive response to MAOIs.

In summary, the recent data indicate that specific atypical depressive and anxiety symptoms are more useful in predicting response to MAOIs than categorical diagnosis of currently defined subtypes. MAOIs may be superior for as yet poorly defined subtypes of depression, which include reversed neurovegetative signs, mood reactivity, interpersonal sensitivity, anxiety, and phobia. It is unclear whether this differential response indicates the existence of subtypes with distinct pathophysiological bases or simply a differential response to side effects and overall antidepressant efficacy (White et al., 1984; Zisook et al., 1985; Joyce and Paykel, 1989). No controlled trials exist that compare MAOIs to selective serotonin reuptake inhibitors (SSRIs) or bupropion, both of which have been used for atypical depression (see Chapter 17).

Major Depression (Unipolar)

A number of early reports in adult patients suggested that heterocyclic compounds were more effective than MAOIs in the treatment of severe or "endogenous" depression, especially when accompanied by melancholia (West and Dally, 1959) (see Chapter 8), while several others concluded that MAOIs were probably equally effective on global outcome measures (Rees and Davies, 1961; Ravaris et al., 1980). Ravaris and associates' (1980) study, cited above, suggests that any difference is probably slight and may be limited to the symptom of insomnia (Ravaris et al., 1980).

More recent studies support the effectiveness of MAOIs for classical major or endogenous depression. Tranylcypromine has been used successfully in open (McGrath et al., 1984) and controlled (Gabelic and Moll, 1990; Rossel and Moll, 1990) trials. L-Deprenyl is superior to placebo at doses that inhibit MAO-A (Mann et al., 1989). Isocarboxazid is less well studied than phenelzine and tranylcypromine but appears to have equal efficacy (Davidson and Turnbull, 1984; Davidson et al., 1988). In direct comparison with TCAs, MAOIs generally show equal efficacy for major depression, although comparison is difficult in many studies due to inadequate doses of one or both agents. Under double-blind conditions, high-dose phenelzine (75 mg/day) was as effective as imipramine in 32 cases (Vallejo et al., 1987) and was more effective and better tolerated than amitriptyline in 29 cases (Raft et al., 1981). Georgotas and associates (1987, 1989)

compared phenelzine to nortriptyline in elderly patients with major depression, verifying adequate dosing of nortriptyline with plasma levels. After 6 weeks phenelzine was as effective as nortriptyline (57.1% vs. 54.5% responders), but after 12 weeks phenelzine (80.9%) was superior to nortriptyline (68.2%) (Georgotas et al., 1987a, 1989). In the study by Kayser and associates (1988) noted above, both melancholic and nonmelancholic major depression responded equally well to phenelzine and amitriptyline, although patients with anxiety and interpersonal sensitivity responded better to phenelzine (Kayser et al., 1988).

Recently, moclobemide has seen more intensive study than traditional MAOIs. In a large, multicenter controlled study of major depression, moclobemide has been shown to be at least equal in efficacy and superior in tolerance to imipramine (Versiani et al., 1989; Biziere and Berger, 1990; Casacchia and Moll, 1990; Ucha Udabe et al., 1990), desipramine (Gabelic and Moll, 1990), and clomipramine (Larsen et al., 1984; Civeira et al., 1990; Dierick et al., 1990; Funke et al., 1990).

In further attempts to find pretreatment markers for antidepressant specificity, abnormal baseline MAO activity has been detected in many psychiatric disorders. Platelet MAO activity has been shown to be higher than normal in unipolar depression and lower than normal in bipolar depression (Demish et al., 1981; Reveley et al., 1981). It has been suggested that high baseline platelet MAO may predict a positive response to MAOIs. However, this effect does not appear to be specific, as Georgotas and colleagues (1987) found that among elderly depressed patients, higher baseline platelet MAO activity predicted antidepressant response to both phenelzine and nortriptyline (Georgotas et al., 1987b). Therefore, high baseline platelet MAO activity may be associated with the severity or manifestation of depression, but does not seem to predict antidepressant specificity.

In summary, current evidence indicates that under research conditions MAOIs are an effective treatment for major or endogenous depression in adults, although TCAs may be more effective at alleviating insomnia. However, MAOIs have not become first-line therapy due to the additional liability of dietary tyramine restriction and risk of the tyramine pressor reaction. Moclobemide has undergone controlled comparisons with tricyclic agents and appears to be equal or superior in efficacy while not conferring significant risk of hypertensive reactions, but is not yet available in the United States. Again, MAOIs have not been directly compared to newer antidepressant agents, such as serotonin-reuptake inhibitors and bupropion.

Bipolar Depression

The depressed phase of bipolar affective disorder is often resistant to treatment with standard tricyclic antidepressants. As noted above, bipolar depression is most often associated with decreased baseline platelet MAO activity, and since elevated MAO activity is purported to be a positive predictor of MAOI response,

bipolar depression might be expected to respond poorly. This is not the case. Furthermore, high platelet MAO activity has also been detected in some bipolar depressed patients who responded to MAOI therapy (Rihmer et al., 1983). Reversed neurovegetative signs are common in bipolar depression, leading to the proposal that bipolar depression should respond to the same agents as atypical depression (Himmelhoch et al., 1991).

Quitkin and associates (1981) reported successful treatment of bipolar depressed patients in open trial with MAOIs. However, few placebo-controlled trials of MAOIs are available. Thase and colleagues (1992) have compared the efficacy of tranylcypromine to imipramine as a first-line agent for bipolar depression and examined the effect of crossing nonresponders over to the opposite medication condition (Himmelhoch et al., 1991). In the first phase of this study, 56 subjects with bipolar depression were treated under double-blind conditions with tranylcypromine or imipramine. Tranylcypromine proved significantly better for both symptom reduction and tolerance (Himmelhoch et al., 1991). In the second phase, 18 patients who had not responded to the initial agents were crossed over to the opposite medication condition. Nine out of 12 patients who had failed imipramine responded to tranylcypromine, and one of the four patients who had failed tranylcypromine, responded to imipramine (Thase et al., 1992).

These data make a strong case for the treatment of bipolar depressed patients with MAOIs if they have failed tricyclic treatment. In the studies above, no increased risk of manic induction was noted with tranylcypromine, but this remains a risk of antidepressant therapy in bipolar patients treated with MAOIs (see Adverse Reactions below).

Child and Adolescent Depression

Very little has been written about the use of MAOIs in childhood and adolescent depression. This can be largely attributed to the risk of tyramine pressor reactions and the difficulty, especially in older children, of maintaining strict dietary control. In addition, depression was not recognized as a significant mental health problem in children until the mid-1970s and Rutter's "Isle of Wight" studies (Rutter et al., 1976), delaying testing of all antidepressant agents in children behind that in adults (Rihmer et al., 1983).

Despite the lack of research, strong arguments exist for testing MAOIs in child and adolescent depression. The frequency of atypical depressive symptoms in adolescents and young adults has led to the proposal that "atypical" depression may, in fact, be the primary manifestation of major depression in young people (Casper et al., 1985; Ryan et al., 1988; Ryan, 1990). Furthermore, controlled studies of tricyclic agents have not supported their efficacy for adolescent depression (Kramer and Feiguine, 1981; Ryan et al., 1986) and only partially support their efficacy in preadolescent children (see Chapter 8) (Razani et al., 1983).

The only two studies of MAOIs in child and adolescent depression are favorable, albeit inconclusive. Frommer (1967) conducted a double-blind, placebo-controlled study of phenelzine combined with chlordiazepoxide in 16 depressed and 15 “phobic” children aged 9–15 years. The clinical descriptions appear to meet criteria for major depression in the first group and separation anxiety/school phobia in the second. Although the groups were merged for analysis, the phenelzine-chlordiazepoxide combination was superior overall to placebo-chlordiazepoxide (Frommer, 1967). In the only other published series, Ryan and associates (1988) conducted a retrospective study of 23 cases of adolescent major depression treated with MAOI. In each case the child had failed a trial of a tricyclic compound and was subsequently treated with either phenelzine or tranylcypromine. If the tricyclic had shown no benefit, an MAOI was used alone. If there had been incomplete response, an MAOI was prescribed in combination with the TCA. When used in this manner, 74% of children responded to treatment, but only 57% both responded and maintained dietary restrictions (Ryan et al., 1988). Of the seven adolescents who became noncompliant with dietary restrictions, one experienced a pressor response and none had serious consequences.

Moclobemide has shown to have efficacy at high doses (mean dose 675 mg/day) against placebo in the treatment of dysthymia. Anticholinergic symptoms and sleepiness were significantly more frequent side effects in a group of subjects receiving imipramine than in those receiving moclobemide or placebo. The investigators’ final overall assessment of tolerability favored moclobemide over imipramine (Versiani et al., 1997).

Conclusions

MAOIs are effective therapy for most forms of depression including major depression with or without melancholia and bipolar depression. Additionally, MAOIs appear to be superior to tricyclic antidepressants for the treatment of depression with prominent anxiety symptoms, especially panic attacks or phobia, and depression with reversed neurovegetative signs. There are only two clinical trials of MAOIs in child and adolescent depression, and few conclusions may be drawn from these data alone. However, on the basis of experience in adults and the frequency of “atypical” symptoms in youngsters, it seems likely that MAOIs would work as well in adolescents as in young adults. Dietary compliance and the availability of prompt medical attention need to be assured. MAOIs can be considered in a child or adolescent who has failed treatment with tricyclic agents and SSRIs. The pending availability of MAOIs that do not require dietary restriction should give rise to new clinical trials in this age group. Sensitivity to dietary tyramine may be reduced by the *cautious* combination of MAOIs with tricyclic antidepressants (see Dosage and Administration below) (Ryan et al., 1988).

Anxiety Disorders

Depression with prominent anxiety or phobia appears to respond better to MAOIs than to TCAs (discussed above). However, since anxiety and phobia are independent targets of MAOI treatment, it is difficult to determine whether this represents a depressive subtype or two comorbid conditions that respond to MAOIs. Clinical trials in patients with comorbid depression and panic attacks show that phenelzine is superior to amitriptyline with roughly equal effects on depression but superior efficacy on anxiety symptoms (Kayser et al., 1988).

Panic Disorder

Reports of the successful treatment of panic attacks with MAOIs date back to the early 1960s (Sargant and Dally, 1962). However, few studies have focused on simple panic (without agoraphobia) as a separate clinical entity. Platelet MAO activity has been tested and found to be significantly lower in panic disorder patients (Balon et al., 1987), although the clinical significance of this finding is unknown. Buigues and Vallejo (1987) treated 35 outpatients with panic disorder or panic disorder with agoraphobia in an open trial of phenelzine. This study is particularly interesting for its stringent definition of drug response. A panic disorder patient was considered a responder only if panic attacks and "subpanic" symptoms ceased completely. Agoraphobics were considered responders if they stopped experiencing anticipatory anxiety and started confronting avoidant behavior *without* behavioral intervention. If additional behavioral treatment was required for success, they were termed partial responders. With these criteria, 34 of 35 patients had remission within 6 months (Buigues and Vallejo, 1987).

Agoraphobia/Social Phobia

In contrast to simple panic, both panic disorder with agoraphobia and social phobia have been comparatively well studied. Agoraphobia may also present without a history of panic attacks and in such cases is difficult to distinguish from social phobia (American Psychiatric Association, 1994). Apart from the presence or absence of panic attacks, all three of these phobic disorders are phenomenologically similar to the childhood diagnosis of separation anxiety, formerly called school phobia. All are frequently associated with depressive and somatic symptoms; each may lead to avoidant behavior aimed at averting a phobic situation, and the severity of each is judged by the degree to which avoidant behavior interferes with normal functioning.

Early clinical trials of iproniazid noted its success in treating panic disorder with agoraphobia (then termed "phobic anxiety") (West and Dally, 1959) and social phobia (Mountjoy et al., 1977). Of interest to child psychiatrists is the early study by Frommer (1967) cited above. One of the two groups successfully treated with phenelzine plus chlordiazepoxide appears to meet current criteria for

separation anxiety/school phobia (Frommer, 1967). However, no other trials of MAOIs in separation anxiety are available.

Most of these early trials were conducted in patients with phobic symptoms plus comorbid generalized anxiety, dysthymia, major depression, or substance abuse. Only recently have studies been restricted to relatively homogeneous phobic syndromes. In open trials, moderate to marked improvement of social phobic symptoms was observed in 79% of 29 subjects treated with tranylcypromine (Versiani et al., 1988) and 100% of 11 subjects treated with phenelzine (Liebowitz et al., 1986).

A few placebo-controlled studies of adults have explored the efficacy of MAOIs using current criteria of social phobia. Liebowitz and associates (1990) compared phenelzine to atenolol (β -adrenergic antagonist) and placebo in 74 subjects. Phenelzine produced a 64% response rate compared to 30% for atenolol and 23% for placebo. They further observed that phenelzine may be more effective when social phobia is generalized to many situations, rather than restricted to specific fears such as performance or public speaking (O'Brien et al., 1992). Gelernter and collaborators compared four treatment conditions for social phobia—cognitive-behavioral therapy, alprazolam, phenelzine, and placebo—in 65 subjects. All groups improved on self-report scales, but the pharmacological agents were superior on physician rating scales for both symptomatic and functional improvement. The phenelzine-treated group achieved the highest rating of functional improvement, although the magnitude over alprazolam was slight (Gelernter et al., 1991). Similarly, a small effect size over placebo was recently reported by Schneier and collaborators in an 8-week double blind study of moclobemide for the treatment of social phobia (Schneier et al., 1992). This study included several adolescents among a sample of 77 subjects. Intention-to-treat response rates at week 8 were 7 of 40 (17.5%) for the moclobemide group and 5 of 37 (13.5%) for placebo (Schneier et al., 1992).

Conclusions

Current data suggest that MAOIs may be as effective as heterocyclic antidepressants and benzodiazepines in the treatment of agoraphobia and social phobia, although insufficient data are available that directly compare these agents in homogeneous patient samples. Only after TCAs and benzodiazepines have failed in cases with serious functional impairment should MAOIs be prescribed, due to the difficulty of dietary compliance and the risk of hypertensive reactions (Modigh, 1987).

The phenomenological similarity between adolescent and adult phobic disorders (agoraphobia without panic attacks and social phobia) and separation anxiety/school phobia in children suggests that reversible agents may also be effective in younger children. The relative success of nonpharmacological treatment of childhood anxiety disorders requires that any pharmacological measures

be of high efficacy and exceedingly low risk, criteria by which reversible selective MAOIs may eventually become the treatment of choice, but by which current MAOIs cannot be recommended.

Attention-Deficit Hyperactivity Disorder

For a clinical description of this childhood disorder, see Chapter 7. Attention-deficit hyperactivity disorder (ADHD) is most often thought of as a disorder of catecholamine underactivity. The therapeutic effects of methylphenidate and d-amphetamine provide indirect support for this concept. In addition, several studies have reported low MAO activity in children with ADHD (Shekim et al., 1982; 1986) and both high and low platelet MAO activity in individuals with high impulsivity (Wender et al., 1983; Tanghe et al., 1997), ADHD with conduct disorder (Bowden et al., 1988), and “thrill seeking” personality characteristics (Af Klinteberg et al., 1987a,b). In one small study, treatment with d-amphetamine returned MAO activity to normal in hyperactive children (Shekim et al., 1982). However, it is important to note that a direct relationship between platelet MAO activity (MAO-B) and central nervous system MAO has not been established (Young et al., 1986). Abnormal platelet MAO activity may be a manifestation rather than a biological marker of hyperactivity and impulsivity.

Whatever the significance of platelet MAO studies, preliminary clinical trials of MAOIs for the treatment of ADHD show promise. Zametkin and associates (1985a,b) compared psychostimulants to several medications alter catecholamine metabolism for the treatment of ADHD. Prompted by open trials in adults with residual ADHD symptoms (Wender et al., 1983; Wood et al., 1983) and by the hypothesis that MAOIs should have an effect on catecholamine systems comparable to that of psychostimulants, this group conducted a double-blind crossover study of MAOIs in 14 boys with ADHD. Both clorgyline (irreversible MAO-A inhibitor) and tranylcypromine “closely paralleled dextroamphetamine effect” (Zametkin et al., 1985a,b). Interestingly, a follow-up study of L-deprenyl (selegiline, an irreversible MAO-B inhibitor) showed less efficacy compared to clorgyline and tranylcypromine in the treatment of ADHD (Rapoport et al., 1985), suggesting that the therapeutic effects on ADHD may also be mediated by MAO-B.

If reversible MAO-A inhibitors (which do not require dietary restriction) prove to be efficacious, for the treatment of ADHD they may become a viable alternative to psychostimulants. Moclobemide was tested in an open trial of 11 ADHD patients who had failed or were intolerant of stimulant treatment. Parent ratings of hyperactivity as well as objective measures of attention and concentration improved substantially (Trott et al., 1992). Although this is an uncontrolled and unblinded study, it should prompt further research of reversible MAOIs in ADHD.

Eating Disorders

Symptoms of eating disorders occur in up to 6% of young females, but the majority of these cases are time-limited. Current estimates place the prevalence of bulimia at approximately 2% and anorexia nervosa at 0.2% of women aged 12–25 years (Agras and Bachman, 1989). The prevalence of eating disorders in men is much lower, with an estimated sex ratio of 9:1. Since the peak age of onset for eating disorders is from the teens to mid-twenties, these disorders are of particular interest to adolescent psychiatrists, especially in light of potentially devastating outcomes. Although severe cases are rare, early outcome studies reported mortality rates up to 19% (Williams, 1958). Of the 460 cases studied by Patton (1988) between 1971 and 1981, 3.3% with anorexia and 3.1% with bulimia proved fatal. Many survivors remain underweight or amenorrheic, and psychiatric comorbidity is common. The most frequent cause of death in anorexia patients is suicide (Patton, 1988).

Anorexia Nervosa

Several psychotropic agents have been tried in the treatment of anorexia nervosa, but no standard pharmacologic therapy has emerged. Antidepressants have received the greatest attention, perhaps due to the strong association of eating disorders with affective disorders. Low platelet MAO activity has been reported in depressed anorectic patients, but not in nondepressed patients (Biederman et al., 1984). Although there are no placebo-controlled studies to date, two open trials of MAOIs in anorexia have reported success. Hudson and associates (1985) reported 10 cases in which a series of antidepressants were tried. MAOIs (phenelzine or tranylcypromine) were tried in 5 cases and were associated with return of body weight to acceptable levels in 2 (Hudson et al., 1985). Another open trial treated 6 anorectic and 12 bulimic women with isocarboxazid. Treatment resulted in no significant weight change but significant improvement in depression, anxiety, and phobic scales (Kennedy et al., 1985). Interpretation of the latter study is hampered by a high dropout rate in the bulimic subjects and initial weights above 85% of expected in 5 of the 14 subjects who completed the trial (115% in one subject). Therefore, weight gain may have been a weak measure of outcome in this sample.

Bulimia

The data for bulimia is somewhat more complete than for anorexia. Several placebo-controlled studies by Walsh and colleagues (1984, 1985, 1988) suggest that MAOIs may be effective in some cases. In 1984 this group studied 35 bulimic women in a single-blind design comparing phenelzine to placebo. High dropout rate was observed due to dietary noncompliance, placebo response, or intolerance of side effects, with only 20 women completing the 10-week trial. Of these, the

phenelzine group showed a fourfold decrease in bingeing behavior and moderate improvement on an "eating attitudes" scale. However, long-term benefit was established in only 3 of the patients receiving phenelzine (Walsh et al., 1984). More pronounced success was reported in a second study by the same group. Thirty of 53 patients completed a double-blind, placebo-controlled trial. A threefold reduction in bingeing was observed among the 14 who received phenelzine, 6 of whom achieved remission (Walsh et al., 1985). More recently, 50 out of 82 patients completed a third trial with a design similar to the 1985 study. Phenelzine again produced a substantial, statistically significant reduction in bingeing and improvement in eating attitudes (Walsh et al., 1988). In both the 1985 and 1988 studies, the effect of phenelzine on associated affective symptoms was discussed. Bulimic subjects who exhibited significant depressive or anxiety symptoms prior to treatment improved on these measures as well as measures of bulimia. Interestingly, the reduction in bingeing behavior was greater among nondepressed patients than depressed ones, although improvement in both groups was statistically significant. In all three studies, often-intolerable side effects and the difficulty of maintaining a low-tyramine diet limited the overall effectiveness of phenelzine.

Conclusions

Eating disorders remain a possible but by no means proven indication for MAOIs. Only 30–40% of the subjects who completed MAOI trials in the above studies achieved long-term remission, with high relapse and dropout rates in the remaining subjects. Therefore, treatment of anorectic and bulimic adolescents with currently available MAOI agents cannot be recommended, since dietary noncompliance is exceptionally high in both eating disorder patients and in adolescents (Ryan et al., 1988). Consideration should be given to clinical trials of moclobemide to circumvent this problem.

Borderline Personality Disorder

Personality disorders are classically resistant to both psychotherapeutic and psychopharmacological intervention. However, borderline personality disorder (BPD) may be amenable to treatment of associated affective symptoms, even if the core behavioral pathology remains intact (Soloff et al., 1991). Although BPD is one of the personality disorders that may be diagnosed in adolescents (American Psychiatric Association, 1994), there are no trials specific to adolescent borderline patients.

Historically, this heterogeneous syndrome has included symptoms from both "neurotic" and "psychotic" categories, including affective lability, chaotic social relationships, high interpersonal sensitivity, impulsivity, and limited psychotic episodes or perceptions. Comorbid affective disorders are common, especially "atypical" manifestations of depression (see description above). An inter-

esting analysis of comorbid depression in BPD and the efficacy of MAOIs is provided by Parsons and colleagues at Columbia University (1989). They propose that the extant literature can be divided into subtypes of BPD, which have different responses to pharmacological agents. Over 300 patients with atypical major depression or atypical intermittent depressive disorder were treated in a double-blind, placebo-controlled crossover design with phenelzine and imipramine. The subjects were rated for number of borderline features and response of depressive symptoms to treatment. In patients with fewer than four borderline symptoms, the two agents were of approximately equal benefit. However, four or more features of BPD predicted a negative response to imipramine and a positive response to phenelzine. Depressed subjects with BPD showed a 91% response rate to phenelzine, 39% to imipramine, and 21% to placebo (Parsons et al., 1989). One additional controlled study reported improvement in affective symptoms with tranylcypromine while pointing out that there was no effect on behavioral control (Cowdry and Gardner, 1988).

Hysteroid Dysphoria

Overlapping with the depressive symptoms of BPD was the proposed depressive subtype “hysteroid dysphoria.” Characteristic symptoms of this subtype included criteria of BPD (impulsivity, histrionic personality features, and chaotic interpersonal relationships) and atypical depression (interpersonal sensitivity and reversed neurovegetative signs) (Kayser et al., 1985). Early controlled studies tested MAOIs for hysteroid dysphoria, demonstrating superiority of phenelzine to placebo, imipramine (Kayser et al., 1988), and amitriptyline (Kayser et al., 1988). However, the diagnostic validity and response of this syndrome to MAOIs is difficult to discern due to the overlap with BPD and atypical depression, both of which appear to respond to MAOIs.

Conclusions

There is evidence that MAOIs may be superior to heterocyclic compounds for atypical depressive disorders. Since BPD often coexists with atypical depression, MAOIs may be potentially useful in these patients. The former term “hysteroid dysphoria” must be considered a variant of atypical depression and has not been validated as a separate clinical syndrome. Regardless of the target symptoms, extreme caution is required in selecting adolescents with BPD patients who are able to comply with MAOI dietary restrictions.

CONTRAINDICATIONS

MAOI treatment is contraindicated in a variety of circumstances, (Table 4) most of which relate to concurrent medical illness or pharmacological treatment. The

TABLE 4 Contraindications to Treatment with Monoamine Oxidase Inhibitors

Inability to maintain dietary restrictions (see Table 8)
Concurrent use of any sympathomimetic agents or other agents known to react with MAOIs (see Table 7)
Concurrent use with other drugs with MAOI activity
Concurrent use of selective serotonin-reuptake inhibitors
Pheochromocytoma
Preexisting liver disease
Preexisting cerebrovascular disease or untreated hypertension
Impending surgery requiring general or local anesthesia (see Table 7)
Asthma when sympathomimetic bronchodilators are unavoidable

primary contraindication for currently available agents is inability of the patient to comply with dietary restrictions. It is advisable to test the ability to comply by reviewing a detailed log of food and beverage for 2 weeks prior to instituting therapy (see Initiating and Maintaining Treatment below).

Additional contraindications are given in Table 4. Most notable are the following: the presence of cerebrovascular disease, which increases the risk of hypertensive consequences, preexisting hepatic disease, which has been associated with impaired tyramine clearance, pheochromocytoma, which causes high levels of endogenous sympathomimetic amines, and pending surgical procedures that will require anesthesia (Table 5) (Physicians' Desk Reference, 2001). If the patient has been treated with any serotonergic agent (including paroxetine, sertraline, buspirone, trazodone, doxepin, or tricyclic antidepressants), a 7- to 14-day "washout" period is required before starting an MAOI (see Drug Interactions below). A 14-day washout is similarly necessary when changing from one MAOI to another (Ryan et al., 1988). Fluoxetine (Prozac™) has an extended elimination half-life requiring at least a 5-week washout period (Physicians' Desk Reference, 2001). Sympathomimetics, either prescribed, in over-the-counter preparations, or through excessive caffeine intake, are contraindicated (Table 5).

SIDE EFFECTS

A discussion of the side effects of monoamine oxidase inhibitors inevitably focuses on the so-called cheese effect, or the hypertensive reaction produced by dietary tyramine in patients treated with classical MAOIs. Raskin (1972) reported a 3.3% incidence of this effect even when dietary restrictions were observed but found other side effects to be quite rare. This section will discuss both the less severe side effects of monoamine oxidase inhibition and the interaction of MAOIs with tyramine and sympathomimetic amines.

TABLE 5 Medications Contraindicated with MAOI Therapy

Degree of caution	Medication	Comments and examples
Common agents absolutely contraindicated	Sympathomimetic amines	Rx—amphetamine and epinephrine analogs; OTC—ephedrine, pseudoephedrine, phenylephrine, and phenylethylamine
	Dextromethorphan	OTC—present in <i>Dristan</i> [®] , <i>Comtrex</i> [®] , and many others; acts via serotonin reuptake blockade
	Selective serotonin—reuptake inhibitors	Rx—fluoxetine, sertraline, paroxetine, etc.; may produce serotonin syndrome (see text)
	Hypoglycemic agents	Rx—potentiates hypoglycemia
	L-Dopa, methyldopa	Rx—enhances pressor effect; dopa present in some food
	Reserpine, tetrabenazine	Rx—similar to serotonin syndrome
	Tryptophan	Rx—serotonin precursor
Anesthetic agents to be avoided	Narcotic analgesics	Reserved to meperidine and other 5HT blockers, but may also prolong action of morphine and barbiturates
	Ketamine	Theoretical risk of cardiovascular toxicity
	Suxamethonium	May prolong or increase neuromuscular blockade
	Local anesthetics	Avoid epinephrine, norepinephrine, cocaine, and analogs
Agents causing adverse reactions in rare cases	Amantadine	Acts as a dopamine agonist, may produce hypertension
	Chloral hydrate	Hypertension reported, mechanism unknown
	Properidol	Hypotension reported
	Fenfluramine	Delirium reported, mechanism unknown
	Guanethidine	May produce hypertension
Agents to be used with caution	Tricyclic antidepressants	See guidelines in text
	Anticholinergics	Potentiation reported in humans, hyperthermia in animals
	Benzodiazepines	Reports of edema, probably safe
	Caffeine	Hypertension and agitation with excessive intake

Rx = Prescription drug; OTC = available without prescription.

Source: Walsh et al., 1988; Blackwell, 1991.

TABLE 6 Dietary Restrictions Necessary for MAOI Therapy

Dietary guidelines	Tyramine ^a (mg/30g)	Comments and examples
Not permitted		
Cheese, aged, ripened, or spoiled	1.0–65.0	Blue, Cheddar, Gruyère
Smoked, pickled, or unfresh fish	0–99.0	Caviar, anchovies, herring
Fermented dry sausage	3.0–45	Pepperoni, salami, summer sausage
Semi-dry sausage	~2.6	Bologna
Beer		
Imported or import-style ale	0.05–0.4	12 oz. of American-style beer contains about 1 mg tyramine.
American-style	0.05–0.1	Especially Chianti (0.76 mg/30 mL)
Red wine, sherry, liqueurs	0.05–0.4	May be acceptable if very fresh
Beef or chicken liver	0–0.3	
Meat extracts	2.9–9.1	Bovril, Marmite, some dry soup bases
Yeast extracts and supplements	2.0–68.0	Regular bakery products are permitted
Sauerkraut	0.6–2.9	Testing done on German products
Unfresh or overripe protein-rich foods	varies	Leftover meats and expired dairy products
Broad beans (e.g., fava beans)	NA	Contains dopa rather than tyramine
Green banana or banana peel	0.2–2.0	Peel also contains dopamine

Permitted in limited amounts			
Processed American cheeses	0–0.15	Up to 1.5 mg of tyramine in a single slice (1oz) of American cheese	
Avocado	0–0.7	Higher levels in overripe fruit and guacamole	
Bananas, fresh	0.02	Avoid overripe fruit and peel	
Soy sauce and variants	~0.05	Safe unless used in very large amounts	
Peanuts and other nuts	?	No documentation of tyramine content	
Raspberries, fresh or in jams	0.3–2.9	Safe in very small servings	
White wine and distilled spirits	?	No documentation of tyramine content	
Chocolate	NA	Contains phenylethylamine	
Need not be restricted			
Yogurt, sour cream, cream cheese, cottage cheese	0–0.3	Avoid homemade or homemade styles and consume very fresh products	
Fresh fish and meats	ND	Do not allow spoilage	
Fresh fruits (except raspberries)	ND		
Figs and raisins	ND	Canned figs may contain tyramine	
Most dried soups and bouillon	ND		

^a Figures based on one ounce (30 g or 30 mL) portions. Up to 6 mg of tyramine may be ingested safely while taking therapeutic doses of MAOIs.

ND = No detectable amount of tyramine; NA = not applicable, contains other pressor agents.

Source: West and Dally, 1959; Mountjoy et al., 1980; Cooper, 1989; Funke et al., 1990; Thase et al., 1992.

Tyramine Pressor Effect

Dietary tyramine in high doses acts as a pseudotransmitter, with stimulant and pressor effects. Since tyramine is a substrate of MAO, MAOI therapy is associated with a 10- to 30-fold increase in sensitivity to these effects (Murphy et al., 1984). Tyramine is a product of bacterial tyrosine metabolism, leading to high levels in aged or unfresh protein-rich foods, such as cheese. In addition, several foods (broad beans, chocolate, banana peel) have high levels of dopamine precursors and other natural pressor agents, which may produce hypertension during MAOI therapy. As little as 6–10 mg of dietary tyramine in a subject taking MAOIs can result in a significant rise in blood pressure, while 20–25 mg may induce a hypertensive crisis (Brown et al., 1989). Normal (unmedicated) volunteers can tolerate 200–400 mg of oral tyramine before blood pressure increases (Simpson and de Leon, 1989).

When this effect was discovered, it was felt that extreme dietary restrictions were necessary. These restrictions have moderated somewhat with experience and more detailed study of tyramine content in foods (McCabe, 1986; Foods, 1989). The list in Table 6 represents a moderately conservative dietary guide. Violation of dietary guidelines or concurrent use of any sympathomimetic agent may result in a hypertensive crisis. Clinically this consists of severe occipital headache, palpitation, neck stiffness, nausea, vomiting, diaphoresis, pupillary dilation, photophobia, and chest pain. Hypertension has, in rare cases, been severe enough to cause intracranial bleeding and death (Blackwell et al., 1967).

The tyramine pressor effect is primarily responsible for the unpopularity of MAOIs in current clinical practice, as well as the main impetus for development of selective, reversible MAOIs. L-Deprenyl and other selective MAO-B inhibitors do not react significantly with dietary tyramine but currently have no application in child and adolescent psychiatry. Irreversible, selective MAO-A inhibitors (clorgyline) react with tyramine to the same extent as phenelzine and tranylcypromine. However, reversible inhibitors of MAO-A (moclobemide) induce only a modest increase in sensitivity (Table 1). Because moclobemide and tyramine compete for MAO binding, much higher doses of tyramine are required to produce hypertension. For example, a 40 mg dose of tranylcypromine increases sensitivity to *intravenous* tyramine up to 162 times normal (Simpson and de Leon, 1989). In contrast, a single dose of moclobemide increases sensitivity to intravenous tyramine only 2–4 times normal. A study of tyramine-enriched food given to subjects taking 600 mg of moclobemide daily indicated that up to 150 mg of tyramine could be ingested safely, compared to 200–400 mg in unmedicated individuals. This amount of tyramine is not found in normal meals (Zimmer et al., 1990). Therefore, the availability of moclobemide and other reversible MAO-A inhibitors may eliminate the main deterrent to MAOI therapy.

The Serotonergic Syndrome

A well-established interaction has been described between fluoxetine and MAOIs, often referred to as the “serotonergic syndrome.” However, the reaction is not limited to this combination, as it has been reported with MAOIs combined with tryptophan (serotonin precursor) and other agents that inhibit serotonin reuptake. The clinical features include mental status changes (confusion, agitation, hypomania), myoclonus, hyperreflexia, tremor, ataxia, diaphoresis, fever, and autonomic dysregulation (Sternbach, 1991). If the patient is also being treated with an antipsychotic, this syndrome may be difficult to distinguish from a neuroleptic malignant syndrome (see Chapter 12). However, serotonergic syndrome does not commonly produce pronounced rigidity, CPK levels over 1000 U/L, or leukocytosis.

Cardiovascular Effects

Goldman and associates (1986) have reviewed and contrasted the cardiovascular side effects experienced in patients treated with heterocyclic antidepressants and MAOIs. They surmise that MAOI therapy is associated with both decreased and increased resting blood pressure (RBP). The decrease in RBP is most notable in subjects who were hypertensive at baseline (Goldman et al., 1986). Symptomatic reduction of blood pressure (i.e., orthostatic hypotension) may present a significant limitation to MAOI use (Goldman et al., 1986; O’Brien et al., 1992). Conversely, in a small but well-controlled sample, O’Brien et al. (1991) found that tranylcypromine treatment had no significant effect on cardiac conduction.

Manic Symptoms

The incidence of mania induced by MAOIs is not established, but it is probably more common in bipolar depressed patients. One of the first case reports was in a 17-year-old boy who developed rapid cycling bipolar affective disorder after treatment with phenelzine (Mattsson and Seltzer, 1981). Cases have also been reported of mania induced by combined MAOIs and TCAs in depressed bipolar patients (de la Fuente et al., 1986).

General Effects

The most common side effect of MAOI use is hypotension (discussed above) and dizziness. Much less common but established adverse effects include insomnia, impotence, edema, weight gain, elevated hepatic enzymes, and overstimulation (jitteriness, tremors, twitching). Psychotic symptoms may emerge or be exacerbated in rare cases (Physicians’ Desk Reference, 2001).

OVERDOSE

Much of the information on MAOI overdose is drawn from the oncological literature, since MAOI agents are used in antineoplastic regimens. The greatest concern to psychiatrists is accidental or intentional overdose. If the patient has also ingested a source of tyramine or sympathomimetics, then an overdosage is treated much like a hypertensive crisis (see below). However, death has been reported from MAOI overdose alone (Physicians' Desk Reference, 2001). Gellman (1966) reported upon the accidental overdose of phenelzine in a 14-month-old girl who became toxic despite prompt induction of emesis with recovery of pill fragments. Periods of deep sedation alternated with unrestrainable agitation and autonomic dysregulation, although blood pressure remained stable. The child recovered after 9 days of observation and intravenous fluid support (Gellman, 1966).

Toxic symptoms reported by the manufacturers include drowsiness, dizziness, mental status changes (agitation, hyperactivity, confusion, or psychosis), headache, seizures, and coma (Physicians' Desk Reference, 2001). Hypotension or hypertension may develop along with hyperreflexia and general autonomic dysregulation (tachycardia, hyperthermia, tachypnea, pupillary dilation) (Kaplan and Sadock, 1991). Toxic blood levels are not established in humans.

ABUSE/DEPENDENCE

MAOIs are not generally considered drugs of potential abuse, although one case of addiction to tranylcypromine has been reported (Briggs et al., 1990).

DRUG INTERACTIONS

In addition to the pressor effect of dietary tyramine and dopamine, the pressor effects of many medications are also increased by MAOI therapy (see Table 5). This includes several over-the-counter cold remedies and allergy preparations. Serotonergic agents are associated with the serotonergic syndrome as described above. Violation of these medication guidelines may result in a hypertensive or serotonergic crisis.

AVAILABLE PREPARATIONS AND COST

Three MAOIs are currently marketed for psychiatric indications in the United States: phenelzine (Nardil™), tranylcypromine (Parnate™), and isocarboxazid (Marplan™). These are available in tablet form only, in 15, 10, and 10 mg sizes, respectively. Isocarboxazid is rated by the FDA as "probably" an effective treatment for refractory depression.

Current average wholesale prices per 100 tablets are as follows: phenelzine, \$32.29; tranylcypromine, \$38.65; isocarboxazid, \$53.97. Therefore, the approximate daily cost (wholesale) for treatment of an older adolescent is \$0.97 for phenelzine, \$1.16 for tranylcypromine, and \$1.62 for isocarboxazid. Generic equivalents are not offered (Prescription Pricing Guide, 1992).

INITIATING AND MAINTAINING TREATMENT

Education about and adherence to dietary and medication restrictions is necessary before starting MAOI therapy. Verbal discussion of restrictions is not sufficient, as the patient may remember little of what is said. It is advisable to provide well-organized and simply written handouts that may be posted at home and referred to frequently. Since a washout period of 7–14 days or more is required when changing from most other antidepressant agents to an MAOI (see discussion above), the authors have found it helpful to use this time to verify the patient's ability to comply with dietary restrictions. For 2 weeks prior to therapy, the patient and his or her parents should adhere to dietary restrictions while keeping a detailed log of all foods and beverages ingested. The physician may then review the log for compliance and counsel the family on any misinterpretations of the guidelines before prescribing an MAOI.

DOSAGE AND ADMINISTRATION

Guidelines in child psychiatry are virtually nonexistent, since these agents are not approved for use in children younger than 16 years. Even in older children it is recommended that prescription start below the adult dose, with one tablet of phenelzine (15 mg) or tranylcypromine (10 mg) daily, rather than three. Dose increases should not be more frequent than every 14 days, since maximal MAO inhibition is achieved 7–14 days after the last change. Weight-adjusted dose schedules are not established for children, although adult studies suggest that 1.0 mg/kg/day of phenelzine is safe and effective (Robinson et al., 1978). Maximum recommended doses for adults and older adolescents are 90 mg (six tablets) of phenelzine daily or 60 mg (six tablets) of tranylcypromine daily, in divided doses. In the trial cited above, an average phenelzine dose of 15 mg twice daily was well tolerated by children aged 9–15 years (Frommer, 1967). Maximum doses and general safety of MAOIs are not established in preadolescent children.

The combination of MAOIs with TCAs was used in several of the adolescent cases reported by Ryan and associates (1988) and was at one time advocated as a superior treatment for refractory depression (Schuckit et al., 1971). To some degree this practice is counterintuitive, especially when one considers that serotonin-reuptake inhibitors are contraindicated in the presence of MAOIs and that tricyclics inhibit both MAO and serotonin reuptake to varying degrees (Kaplan

and Sadock, 1991). Nevertheless, there are reports of safe treatment in both open (Schuckit et al., 1971; Foods, 1989) and controlled (White et al., 1980; Razani et al., 1983) trials. Not all of these have been favorable, as one study found trimipramine alone to be superior to MAOIs alone and combined with trimipramine in mild to moderate outpatient depression (Young et al., 1979). Another study found electroconvulsive therapy (ECT) to be superior to a phenelzine-amitriptyline combination in severe inpatient depression (Davidson et al., 1978). Likewise, in a double-blind, placebo-controlled trial of 60 patients with major depression, comparing amitriptyline, tranylcypromine, and the two drugs combined, no evidence for increased effectiveness was found (Razani et al., 1983).

Recently, a group of 25 adult and adolescent patients received an open trial with the association of isocarboxazid and amitriptyline. Responders were followed during 3 years ($n = 12$), and every 6 months an attempt was made to discontinue the MAOI. At the end of the study, 4 patients maintained response with single medication, 6 still required both drugs, and 2 relapsed. No clinical differences were apparent between the outcome groups (af Klinteberg et al., 1987a). Overall the combined MAOI-TCA therapy has not been proven to be more effective than single agent therapy, has a higher incidence of adverse side effects, and increases the risk of the serotonergic syndrome with certain agents (Lader, 1983). Combined treatment may or may not increase the risk of cardiotoxic effects (Lader, 1983; O'Brien et al., 1991,1992).

If used in combination TCAs should not be given to a patient who is already taking MAOIs, since it is impossible to predict or control the effect of amine reuptake inhibition in the presence of >80% MAO inhibition. Rather, the MAOI must be discontinued and 14 days allowed for MAO activity to return to normal. Both agents may then be started at very low doses and titrated according to response and the emergence of side effects.

MANAGEMENT OF SPECIFIC SIDE EFFECTS

Hypertensive Crisis

Ryan and colleagues (1988) reported several cases in which adolescents treated with MAOIs intentionally violated dietary guidelines. Even with good compliance, patients may forget about certain forbidden foods or inadvertently ingest foods that they did not realize were rich in tyramine. Extensive premedication counseling is necessary so that the symptoms of a pressor response (headache, diaphoresis, stiff neck, nausea, and vomiting) will be promptly recognized (Kaplan and Sadock, 1991). Patients in remote locations or without access to emergency medical services should probably not receive MAOIs. Chlorpromazine has been used as a short-term treatment measure, leading to the recommendation that several 50 mg tablets (25 mg for children) be provided for patients to

take if symptoms appear, especially if they would be temporarily away from medical care (Ryan et al., 1988; Kaplan and Sadock, 1991). More recently, nifedipine, a calcium channel blocker has also been shown to be rapidly effective (Af Klinteberg et al., 1987b). Patients taking MAOIs could conceivably carry this medication with them at all times and use it in the event of a hypertensive crisis.

The manufacturers recommend immediate discontinuation of MAOIs if a hypertensive crisis is suspected and the use of intravenous phentolamine (5 mg) to treat symptomatic hypertension. Hospitalization with any indicated supportive and symptomatic measures may be necessary. *Dietary and medication restrictions must be maintained for 2 weeks after discontinuation of an MAOI and during treatment of a hypertensive reaction.*

Serotonin Syndrome

A recent review has recommended several steps to be taken when the serotonin syndrome is suspected (Sternbach, 1991). Hospitalization and prompt discontinuation of the medications that are thought responsible is followed by assessment of supportive needs. This may include cooling blankets for fever or ventilation for respiratory depression. Myoclonus, seizures, and agitation have been reported and may require pharmacological treatment. If hypertension is present, nifedipine may be useful. Propranolol has been suggested as an adjunctive agent, since it may provide both symptomatic relief and act as a serotonin antagonist.

Cardiovascular Effects

Hypotension is often tolerable or may be managed with increased fluids and salts. Decreasing the dosage may help but may also influence the effectiveness of the drug. If the patient was hypertensive prior to treatment, any antihypertensive agents should be discontinued. Despite these interventions, a number of patients will be unable to continue MAOI therapy due to symptomatic hypotension. Although hospitalization with intravenous fluids may be necessary in severe cases, *pressor agents are to be completely avoided* (Physicians' Desk Reference, 2001).

HOW TO WITHDRAW MEDICATION

Withdrawal symptoms have been described with MAOIs, but the mechanism of such symptoms is difficult to conceptualize. Upon abrupt discontinuation, monoamine oxidase activity returns to normal gradually over 2 weeks, suggesting that any withdrawal is related to non-MAOI properties of the compound itself. Nevertheless, symptoms have ranged from anxiety and agitation to frank psychosis and have been compared to stimulant withdrawal (Joyce and Paykel, 1989). Gradual discontinuation of the medication is recommended (Physicians' Desk Reference, 2001). Regardless of how the medication is discontinued, monoamine oxidase

activity is suppressed for up to 2 weeks after the last dose, necessitating full compliance to dietary and medication restrictions for that period of time.

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12

Antipsychotic Agents

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INTRODUCTION

Although a mainstay of chemotherapy in adults, antipsychotic agents (also called neuroleptics or “major tranquilizers”) are far less commonly used in child and adolescent psychiatry. Only seven typical agents have Food and Drug Administration (FDA) approval for psychiatric indications in children younger than 12 years. The main causes for controversy are the potentially severe neurological and developmental sequelae of long-term use and the risks of unpleasant short-term side effects, which may hamper learning, socialization, and affect. Therefore, their use is appropriately limited to debilitating psychiatric illness and duration of treatment is as short as possible.

Parallel to these constraints, we are witnessing a period of rapid change in the use of neuroleptics in children, as evidenced by the replacement of conventional antipsychotics by novel antipsychotics as the drugs of choice for first episodes of psychosis and other indications. Increasingly, child psychiatrists in the United States are using risperidone, olanzapine, quetiapine, and ziprasidone in their clinical practice, not only as first-line treatments for schizophrenia, but also for syndromes such as autistic disorder (Fisman and Steele 1996; Fisman et al. 1998), Tourette’s syndrome, and bipolar disorder. This broad shift in the use of

novel antipsychotics in child psychiatry needs to be critically assessed, as the short-term and long-term efficacy and safety profile of these agents in children remains for the most part still unknown.

CONVENTIONAL (TYPICAL) ANTIPSYCHOTIC AGENTS

Chemical Properties

The prototype antipsychotic is the phenothiazine chlorpromazine (Thorazine™), discovered over 50 years ago during the synthesis of potential antihistaminic compounds. Since that time several “atypical” neuroleptics agents have been developed in an effort to improve efficacy and minimize unwanted effects. Neuroleptics may be classified by either chemical structure or relative potency at target receptors (Table 1). Antipsychotic agents bind to a number of receptor sites, including dopaminergic, muscarinic cholinergic, serotonergic, α -adrenergic, and histaminic (Peroutka and Snyder 1980). Most are lipophilic and achieve high central nervous system (CNS)–to–plasma concentration ratios. Although clinical potency correlates best with affinity for dopaminergic receptors (Farde et al. 1992), these agents often bind to other receptor populations with equal or greater affinity, accounting for common side effects (Creese et al. 1976; Seeman et al. 1976). For example, the sedative property of antipsychotics is likely mediated by adrenergic blockade, and the most potent α -adrenergic inhibitors (thioridazine, chlorpromazine, clozapine, and droperidol) are also the most sedating neuroleptics (Peroutka et al. 1977) (Table 2).

Central nervous system dopamine receptors vary in both form and function. Traditionally, clinical potency has been thought to correlate directly with a neuroleptic’s antagonist potency at the type-2 dopamine receptor (D_2). Recent data suggest that this concept is oversimplified. Clozapine has emerged as one of the more effective antipsychotics available in adult schizophrenia, yet it possesses an *in vitro* affinity for D_2 which is only 11% of chlorpromazine and 0.5% of fluphenazine (Table 1). Two recent studies using position emission tomography (PET) and single photon emission tomography (SPECT) to measure *in vivo* D_2 binding showed that traditional neuroleptics occupy 70–89% of D_2 receptors while clozapine occupies only 38–63%. Extrapyramidal side effects were more strongly correlated with D_2 occupancy than were clinical effects (Farde et al. 1992). Despite lower D_2 occupancy *in vivo*, clozapine appears to be clinically superior to traditional neuroleptics while conferring much lower risk of extrapyramidal side effects (Pilowsky et al. 1992).

Currently, at least five subpopulations of dopamine receptor have been isolated in the human central nervous system (D_1 – D_5), with additional genetic variants identified (Grandy et al. 1991; Vahid-Ansari et al. 1996). Of these, clozapine has the greatest affinity for D_4 (Coward 1992). Taken together, these new data

TABLE 1 Relative Potencies of Neuroleptics in Clinical Use and at Dopaminergic and Muscarinic Cholinergic Neuroreceptors

Compound	Trade name	Clinical potency ^a	D ₂ affinity ^a	mACh affinity ^b	Dose range for adults (mg/day)
Phenothiazines					
Chlorpromazine	Thorazine [®]	1	1.0	330	400–1000
Thioridazine	Mellaril [®]	1	0.72	1300	200–800
Mesoridazine	Serentil [®]	2	1.0	330	100–400
Trifluoperazine	Stelazine [®]	30	7.2	35	15–40
Fluphenazine	Prolixin [®]	50–100	24	13	2.5–10.0
Perphenazine	Trilafon [®]	10	13	16	16–64
Prochlorperazine	Compazine [®]	7	2.6	43	30–150
Thioxanthenes					
Chlorprotixene	Taractan [®]	1	2.5	—	100–600
Thiothixene	Navane [®]	25	42	8.1	20–60
Indolic compounds					
Molindone	Moban [®]	10	0.16	0.062	50–225
Diphenylbutylpiperadines					
Pimozide	Orap [®]	50 ^c	5.3	—	1–10
Butyrophenones					
Haloperidol	Haldol [®]	50	2.7	1.0	1–15
Droperidol		—	~6.2	—	~8
Dibenzoxapines					
Loxapine	Loxitane [®]	7	0.26	52	60–250
Clozapine	Clozaril [®]	~1	0.11	2000	300–900

^a Clinical potency and affinity for dopamine type-2 receptors expressed as ratios to chlorpromazine (Klein et al. 1980; Kane et al. 1999).^b Affinity for muscarinic cholinergic receptors expressed as ratios to haloperidol (Klein et al. 1980; Kane et al. 1988).^c From Kapur et al. 1999.

TABLE 2 Relative Potency of Neuroleptics for Common Side Effects

Compound	Sedative	Anticholinergic	Extrapyramidal
Phenothiazines			
Chlorpromazine	High	High	Low
Thioridazine	High	High	Low
Trifluoperazine	Medium	Medium	High
Fluphenazine	Medium	Medium	High
Thioxanthenes			
Thiothixene	Low	Low	High
Diphenylbutylpiperidines			
Pimozide	Low	Low	High
Butyrophenones			
Haloperidol	Low	Low	High
Dibenzoxapines			
Clozapine	High	High	Low

Source: Adapted from Keks et al. 1989.

suggest that antipsychotic response in adults with schizophrenia is only indirectly related to D₂ receptor blockade and that selective pharmacological agents may be able to reduce psychotic symptoms without substantial extrapyramidal side effects.

Absorption and Metabolism

Although absorption and metabolism of neuroleptics have been widely studied in adults, scant data are available in children. In the absence of data on children, the practitioner must presume a higher rate of absorption for oral medications, lower rate of plasma protein binding, lower percentage of body fat distribution (for lipophilic drugs), and more rapid enzymatic metabolism in pre pubescent children than in adults. Therefore, higher mg/kg doses of antipsychotics may be required in children than adults to achieve comparable plasma levels (Potenza et al. 1999). Based on these metabolic differences alone, one would suspect that children should receive higher mg/kg doses than equivalent adult doses before declaring therapeutic failure of an agent. However, Teicher and Glod (1990) correctly point out that in the few pharmacokinetic studies available, individual variability in metabolism is far greater than the developmental variability seen across age groups.

Metabolism of antipsychotics is hepatic, yielding a substantial first-pass effect for oral preparations and wide variability in plasma level for a given mg/kg dose. In adults, oral doses of phenothiazines, thioxanthenes, and butyrophen-

nones reach peak plasma level 2–3 hours after ingestion. Intramuscular injections reach peak levels in 30–60 minutes (Dahl 1990). Metabolites of neuroleptics are excreted primarily through the urine and, to a lesser extent, in bile. Steady state levels of chlorpromazine have been shown to be 2–3.5 times lower in children than in adults for mass-equivalent dose (Dahl 1990). In adults, elimination half-lives of most neuroleptics are in the 10- to 30-hour range. A marked exception is pimozide, the half-life of which has been shown to vary from 24 to 142 hours in preadolescent children and 50 to 200 hours in adults (Sallee et al. 1987). The metabolism of clozapine, a dibenzodiazepine derivative (Birmaher et al. 1992), and other atypical neuroleptics is reviewed in detail below. Unstudied in children, the half-life of clozapine in adults is 10–16 hours (Cheng et al. 1988).

The relationship of plasma level to clinical response is unclear and is currently rendered academic by the lack of readily available and affordable clinical assays. Smith et al. (1979) demonstrated that when compliance was insured, peak and steady-state levels of butaperazine, thioridazine, and haloperidol were significantly lower in chronic nonresponding schizophrenic adults compared to treatment responders (Smith et al. 1979). This suggests that some portion of treatment failures is due to increased rates of drug clearance and inadequate plasma levels. A simple dose-response relationship has not been described for most neuroleptics, but available data do suggest basic dosing guidelines (AHFS 2001).

General Indications

Antipsychotics are, of course, indicated primarily for treatment of psychosis, and their use for childhood psychosis parallels that in adults. Other pediatric indications include Tourette's syndrome and short-term symptomatic treatment of agitation, irritability and severe self-injurious behavior or aggression. Probable indications include pervasive developmental disorders, severe, treatment-resistant attention deficit hyperactivity disorder, and a variety of uses in pediatric medicine (Tables 3 and 4). Despite these fairly narrow indications, neuroleptics have been tried for most psychiatric diagnoses, including generalized anxiety and nonspecific behavioral problems. Antipsychotic use in anxiety disorders is limited to cases that have defied standard treatment and have severe functional consequences. In adults, antipsychotics have seen use in personality disorders, but both the diagnosis and treatment of personality disorders in children remain controversial. Some agents have been used but not systematically studied for child and adolescent obsessive-compulsive disorder.

Schizophrenia

The term "childhood schizophrenia" has undergone several changes since its first use in the early 1900s. The first descriptions were based on adult symptomatology, altered only to account for developmental stage (Kanner 1971). Bender

TABLE 3 Psychiatric Indications and Approved Age Ranges for Conventional Neuroleptic Agents^a

Compound	Age range	Approved indications	Recommended pediatric doses
Chlorpromazine	≥6 months	Psychosis, SBD, ADHD, mania ^b	0.25 mg/kg PO q4–h6 or IM q6–8h. Max IM dose is 45 mg/day (≤5 yr) or 75 mg/day (5–12 yr).
Thioridazine	≥2 yr	Psychosis, SBD, ADHD	0.5 mg/kg/day divided BID or TID to max of 3.0 mg/kg/day in ages 2–12 yr.
Trifluoperazine	≥6 yr	Psychosis, NPA	1–15 mg/day given BID or TID.
Prochlorperazine	≥2 yr	Psychosis, NPA	2.5 mg PO/PR, BID or TID to max of 20 mg/day (2–5 yr) or 25 mg/day (6–12 yr).
Chlorprothixene	≥6 yr	Psychosis	10–25 mg PO TID or QID. IM route not recommended for under 12 yr.
Pimozide	≥2 yr ^c	Tourette's syndrome	1–2 mg/day in divided doses. Max is lessor of 0.2 mg/kg/day or 10 mg/day.
Haloperidol	≥3 yr	Psychosis, ADHD, Tourette's, SBD	0.05–0.15 mg/kg/day divided BID or TID for psychosis or 0.05–0.075 for others.

^a Neuroleptic drugs not listed are not recommended for use under 12 years of age. Loxapine and clozapine are not recommended under 16 years. Pediatric doses are not established for these agents.

^b Abbreviations are as follows: SBD—severe behavioral disorders; MR—mental retardation; ADHD—attention deficit/hyperactivity disorder; NPA—non-psychotic anxiety.

^c Safety of pimozide in children under 12 years of age is not well established.

TABLE 4 Nonpsychiatric Pediatric Indications for Conventional Neuroleptic Drugs

Compound	Trade name(s)	Approved ages	Approved indications
Prochlorperazine	Compazine®	≥2 yr	Nausea/vomiting
Thiethylperazine	Norzine® Torcan®	≥2 yr	Nausea/vomiting
Metoclopramide	Reglan®	Any	Nausea/vomiting
Chlorpromazine	Thorazine®	≥6 months	Nausea/vomiting Intractable hiccups Preop restlessness or anxiety
Trimethobenzamide	Tigan®	Any	Nausea/vomiting
Perphenazine	Trilafon®	≥12 yr	Nausea/vomiting
Promethazine	Phenergan®	≥2 yr	Nausea/vomiting Motion sickness Allergic reactions Preop, postop, and obstetric sedation
Promethazine + meperidine (narcotic)	Mepergan®	Any	Sedation and sleep Preanesthetic sedation Adjunct to general or local anesthesia

(1947) initiated a trend to include child cases that did not exhibit what are now termed “Schneiderian first-rank” symptoms of schizophrenia. Such child cases are now largely subsumed within the diagnoses of pervasive developmental disorder (PDD) and schizoid or schizotypal personality disorders (Bender 1947; Faraone 1979; APA 1987). These early criteria produced an estimated prevalence for childhood schizophrenia of 1.4–4.5 per 10,000 (aged <13 years) (Bomberg et al. 1973; Kramer 1978). The diagnosis of schizophrenia in children is now reserved for cases in which adult criteria are met (APA 1987). Based on this definition, Burd and Kerbeshian (1987) reported the existence of only two cases of schizophrenia in North Dakotan children aged 2–12 years (approximately 0.19 per 10,000) (Burd and Kerbeshian 1987).

Despite the current application of adult criteria, phenomenological differences between child- and adult-onset schizophrenia do exist. The distinction is pertinent for interpretation of early medication trials, the persisting diagnostic confusion between schizophrenia and PDD, and the differential response of these entities to antipsychotic medication. When it appears after puberty, schizophrenia is comparable to the adult syndrome. However, in prepubescent children the diag-

nosis is more complicated. The frequency of visual hallucinations appears to be higher in child than in adult schizophrenia (Kolvin et al. 1971), while hallucinatory experiences in general may be less frequent in schizophrenic children younger than 8 years (Jordan and Prush 1971). Most writers have emphasized developmentally inappropriate formal thought disorder, poorly organized delusional systems, ideas of reference, poor affective regulation, and impaired social functioning as the most selective clinical signs (Beitchman 1985). A single sign in this constellation does not seem to predict an eventual diagnosis of schizophrenia, as many normal developmental phenomena may be construed as psychotic by adult standards, such as "imaginary friends," irrational concern about parental safety, and illogical beliefs. Kotsopoulos et al. (1987) have reported a high frequency of hallucinations (1.1% of psychiatric consults) in children served in a large pediatric outpatient department, none of whom had schizophrenia and all of whom were effectively treated without antipsychotic medication.

Once the diagnosis of schizophrenia is established in a child or adolescent, treatment guidelines parallel those established in adult schizophrenia. This is due more to the lack of controlled studies in children than to proven strategies. In the acute phase of adult schizophrenia, all commonly prescribed antipsychotics are superior to placebo in treating psychosis (May et al. 1976; May et al. 1976a,b; Klein et al. 1980; Richelson 1990). Maintenance treatment with neuroleptics is likewise superior to placebo in prevention of relapse, and is influenced by the preservation of social supports and lowered emotional demand (Hogarty et al. 1974).

In one of the few placebo-controlled trials in children, Campbell et al. (1972) compared chlorpromazine to lithium in 10 "severely disturbed" children, 6 of whom were diagnosed with schizophrenia. All of the children with schizophrenia improved when treated with chlorpromazine based on exam by a psychiatrist (nonblind); one improved markedly (Campbell et al. 1972). These changes did not reach statistical significance in blind measurements, but analysis included all 10 subjects and was not separately reported for the 6 with schizophrenia. Similarly, Spencer et al. (1990) reported the preliminary results of a double blind, placebo-controlled study of haloperidol in 7 schizophrenic children, which showed marked benefit.

More recently, Frazier et al. (1994) conducted the first 6-week open clozapine trial (mean daily dose 370 mg) of 11 adolescent with childhood-onset schizophrenia. This study was followed by a double-blind, parallel-group controlled study of clozapine versus haloperidol in children and adolescents with childhood-onset schizophrenia conducted by Kumra and colleagues at the NIMH (Kumra et al. 1996). Both of these studies are reviewed in more detail below.

The manifestations of schizophrenia have classically been divided into pos-

itive symptoms (hallucinations, delusions, ideas of reference, and formal thought disorder) and negative symptoms (withdrawal, flattening of affect, amotivation, and apathy) (Meltzer 1989). While typical antipsychotic agents are unequivocally effective against the positive symptoms (i.e., psychosis), the question of whether they successfully treat negative symptoms remains undecided. The contribution of specific antipsychotic side effects to negative symptoms of schizophrenia will be discussed below.

Case History*

R. was a 13-year-old postpubertal girl who had exhibited a 6-month deterioration in functioning that initially consisted of avoidance of group activities, deterioration in school performance, and refusal to complete school assignments. Later she began to refuse to prepare herself for school, and for 6 weeks she had exhibited even more unusual behavior. She would sit, laughing for no apparent reason, and appear to be listening to something. She felt people watched her and laughed at her. She believed she smelled and took numerous showers. Within the family, she became increasingly hostile, particularly toward her younger sister. Her handwriting deteriorated. She wrote notes to her friends remarking on her persecution and torment. A few days prior to admission to a psychiatric hospital, she suddenly refused to enter the bathroom, believing that she was being spied on from outside. She gradually became increasingly upset and tearful, talked of God and the Devil speaking to her, and wished to die to end her persecution.

R. was the product of a liaison her mother had outside the marriage while separated from her husband. R. was, therefore, a half-sister to three of her siblings (30-year-old brother, 28-year-old sister, and 26-year-old brother) and had a full sister one year younger than herself. R.'s mother later reconciled with her husband. The mother was a high school graduate. She was overtalkative, bossy, and irritable with R. The maternal grandmother had received psychiatric treatment. The natural father was a convert to fundamentalist religion who lived with his own family in another state. He was not in contact with R. The stepfather was a railroad foreman who seemed calm and appropriate in managing the family situation.

Although the birth history was unremarkable, R. had respiratory problems at 2 weeks of age, which almost led to a crib death. She was cyanotic and required resuscitation. In a nonspecific way, she had always been considered "weak" and sensitive. For example, she required to be walked to sleep throughout her toddler years. She had been placed on tranquilizers for hyperactivity from 18 months to 4 years. There were no reported delays in development, and R. was

* From Pomeroy 1990.

a competent student prior to her illness. However, she had appeared less mature and “sillier” compared to her peers. Psychological testing (after her illness began) revealed a WISC-R full-scale IQ of 90 with verbal and performance scales identical at 91.

Examination of her mental state showed a tall, heavy 13-year-old girl with slow, rigid gait and an air of confusion. Affect was mostly flat, but she had bouts of inappropriate giggling. Her thought patterns showed marked blocking, but other than a slow and deliberate speech she did not exhibit other thought disorders. She described numerous psychotic symptoms. She felt controlled by God and the Devil, and believed she was being watched. She had auditory, olfactory, tactile, and possibly visual hallucinations. She believed thoughts were inserted into her head and that others would read her mind. The only significant physical findings were orthopedic abnormalities (thoracic kyphosis, lumbar lordosis, and spina bifida occulta).

Pharmacological therapy with haloperidol significantly reduced the psychotic phenomena, and behavioral management techniques were used to address continuing unusual behaviors secondary to her delusional ideas. Because of extrapyramidal side effects, pharmacotherapy was changed to trifluoperazine. On discharge from the hospital, R. continued to have a flat affect and occasional psychotic experiences. In addition, family stresses were apparent. She was referred to a therapist who focused on these family problems and withdrew the medication. R. rapidly returned to her earlier psychotic state and did not respond at the time of follow-up to reinstitution of neuroleptic therapy.

Transient Psychoses

Transient psychotic symptoms are associated with affective disorders such as major depression and bipolar disorder, psychoactive drug overdose, non-schizophreniform paranoid disorders, and organic mental disorders. Paranoid disorders are rarely diagnosed in children, largely due to the difficulty differentiating transient psychotic symptoms from normal developmental phenomena. However, drug abuse and organic mental disorders are encountered. Although the use of neuroleptics in such cases has not been systematically studied, case studies and clinical practice have demonstrated their effectiveness under certain conditions.

Neuroleptics are useful during acute intoxication with psychoactive drugs, especially hallucinogens and phencyclidine (PCP). High-potency agents (haloperidol) in low doses are preferable. However, neuroleptics are contraindicated for sedative overdose and during withdrawal states, as they may further depress consciousness or mask life-threatening withdrawal symptoms. Low-potency agents are not generally useful due to their anticholinergic properties, especially in cases

of delirium in which anticholinergic agents may be a suspected cause (Ellinwood et al. 1990).

Delirium is distinguished from other psychiatric diagnoses by relatively rapid onset, the presence of a fluctuating level of consciousness, and a known or inferred medical or neurological cause. Thought is disorganized and the ability to maintain attention is impaired. Sleep/wake cycles are nearly always disrupted, and psychotic symptoms such as hallucinations, formal thought disorder, illusions, and delusions are often present. Diffuse background slowing on electroencephalogram may help distinguish delirium from other mental syndromes, especially if a previous EEG is available for comparison. Pediatric causes include direct brain injury, CNS neoplasms, Addison's disease, Wilson's disease, hyper- or hypothyroidism, and other metabolic disorders (Kaplan and Sadock 1991). There are no controlled studies of neuroleptics for these disorders in children, but their use in adult causes of delirium is well documented. Low-dose haloperidol was favored due to its minimal anticholinergic activity (May et al. 1976a,b). Intravenous haloperidol combined with a benzodiazepine has been advocated in hospitalized, medically ill adults with delirium on the basis that it provided superior response with fewer extrapyramidal side effects (Adams 1988; Menza et al. 1988).

Tourette's Syndrome

Gilles de la Tourette described this syndrome of chronic motor and vocal tics in 1885. Current standards define a tic as "an involuntary, sudden, rapid, recurrent, non-rhythmic, stereotyped motor movement or vocalization. It is experienced as irresistible, but can be suppressed for varying lengths of time" (APA 1987).

Although several tic disorders are recognized, only Tourette's syndrome is an approved indication for treatment with neuroleptic agents. Therefore, care must be taken to distinguish Tourette's from other chronic or transient tic disorders. A diagnosis depends on the presence of multiple motor tics (involving more than one muscle group) and at least one phonic tic, onset before age 21, and persistence of symptoms beyond one year (APA 1987). More stringent diagnostic criteria have been suggested and are often used in clinical trials, narrowing the age of onset to between 2 and 15 years and requiring the presence of more than one phonic tic (Leckman and Cohen 1990). Both motor and phonic tics may take virtually any form. Simple motor tics usually appear early in the disorder and may include eye blinking, facial grimacing or twitching, shoulder shrugging, or head turning. A simple phonic tic is any respiratory movement that produces a sound, such as grunting, coughing, sighing, sniffing, throat clearing, or unintelligible vocalizations. Complex tics typically arise later in the syndrome and may include complex motor movements and intelligible words. The most recognized symptom of Tourette's syndrome is "coprolalia," or the involuntary utterance

of obscenities. Despite its infamy, coprolalia appears in only 20–40% of cases (Leckman and Cohen 1990).

Other disorders may mimic Tourette's and must be ruled out before initiating a trial of neuroleptics. If the tics emerged during treatment with psychostimulants for attention-deficit hyperactivity disorder (ADHD) or with sympathomimetics for asthma, these agents should be discontinued to ensure that the syndrome is not pharmacologically induced. A portion of such cases will have persistent symptoms, but whether psychostimulants can cause Tourette's or simply speed its emergence in susceptible individuals is unknown (Gadow et al. 1995). If the repetitive movements are complex, they may be indistinguishable from the behavioral symptoms of obsessive-compulsive disorder and this diagnosis must be considered (Jagger et al. 1982). The possibility of partial complex seizures should be ruled out with serial electroencephalograms. However, non-specific EEG abnormalities are not contrary to the diagnosis, since they occur in as many as half of Tourette's cases (Leckman and Cohen 1990).

Two antipsychotic agents are approved for use in Tourette's syndrome: haloperidol (Haldol™) and pimozide (Orap™). The effectiveness of each has been well demonstrated in a number of placebo-controlled studies (Siever 1981; Gillies and Forsythe 1984; Caine 1985; Shapiro et al. 1987; Kerbeshian and Burd 1988), but the two agents have not been compared to each other in a double-blind, placebo-controlled design. Sandor et al. (1990) reported long-term experience with a retrospective cohort of Tourette's cases treated with haloperidol, pimozide, or no medication over a period of 1–15 years (Sandor et al. 1990). The pimozide group had significantly fewer adverse side effects, and the haloperidol group showed a higher rate of noncompliance, suggesting that pimozide may be more clinically effective despite equal efficacy at symptom reduction.

Tourette's is associated with a number of nonspecific behavioral symptoms, such as increased impulsivity, low frustration tolerance, poor concentration and academic performance, impaired social development, and motoric hyperactivity (Leckman and Cohen 1990). A concurrent diagnosis of ADHD is common. For cases in which behavioral symptoms predominate, clonidine should be considered as an alternative to pimozide or haloperidol (Connor et al. 2000). Stimulants (methylphenidate, *d*-amphetamine, pemoline) are overall contraindicated in Tourette's as they greatly increase the severity of tics, especially for higher doses of dextroamphetamine (DEX) compared to methylphenidate (MPH) (Gadow et al. 1995).

Risperidone also appears to be effective in reducing tic frequency and intensity in children and adolescents with chronic tic disorders as evidenced by a pilot 11-week open-label trial involving five patients with Tourette's syndrome and two with chronic motor tic disorder (mean age of 12.9 years). Three children had a comorbid diagnosis of obsessive-compulsive disorder (OCD). The patients, seen at baseline and for two follow-up visits, received a maximum maintenance

dose of 2.5 mg/day of risperidone in divided dose, achieved on average by week 3. The Yale Global Tic Severity Scale and the children's version of the Yale-Brown Obsessive Compulsive Scale revealed a statistically significant reduction in tic scores between the baseline and each subsequent visit. One of three children with comorbid OCD showed substantial improvement. All seven subjects gained weight, ranging from 8 to 14 lb, during risperidone treatment (Lombroso et al. 1995).

Pervasive Developmental Disorder

Autism was initially thought by Kanner to be a distinctive manifestation of schizophrenia in childhood (Kanner 1943), but he later abandoned this idea in favor of separate classification (Kanner 1971). The issue was actively debated until the late 1970s, when clinical, epidemiological, and neurophysiological evidence made a conclusive case for autism as a unique clinical entity (Minshew and Payton 1988). DSM-III-R now includes autistic disorder as the primary diagnosis under the category of pervasive developmental disorder (APA 1987). Because of the early diagnostic confusion and greater prevalence, more clinical trials of neuroleptics have been conducted in autism than in childhood schizophrenia. Subjects studied in early "schizophrenia" trials must be considered a mixed diagnostic group of developmental disorders and psychosis, limiting their usefulness.

A diagnosis of autistic disorder is based on a clinical triad of abnormal development. The child must demonstrate marked impairment in reciprocal social interaction, characteristic abnormalities in verbal and nonverbal communication, and a restricted range of spontaneous interests. After 50 years of research, this definition remains difficult to operationalize. Recent attempts to standardize diagnosis of autism across research sites have led to the development of standardized diagnostic instruments, such as the Autism Diagnostic Interview (ADI) (Le Couteur et al. 1989) and Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1989). More clinically based instruments, such as the Childhood Autism Rating Scale (CARS), may aid in diagnosis (Schopler et al. 1988). However, most medication trials in autistic subjects lack standardized methods, and results should be interpreted in light of probable diagnostic heterogeneity (Sloman 1991).

Before reviewing the efficacy of neuroleptics in the treatment of autism, it is important to determine what aspects of the disorder are targeted. Autistic children display a broad range of developmental and behavioral pathology, little of which can be expected to respond to pharmacological intervention (Gualtieri et al. 1987). Of the core symptoms, treatment has focused on increasing spontaneous social interaction and communication skills. Associated symptoms that may respond to medication include behavioral impulsivity, hyperactivity, self-injury, and stereotypy. In all cases the goal of treatment is to ameliorate or compensate for individual symptoms rather than to cure autism (Sloman 1991).

Magda Campbell and colleagues were most active in evaluating neuroleptics for this disorder. In the study cited above, only one of the 10 “severely disturbed” children was diagnosed with autism. That child was judged to have improved slightly on chlorpromazine (Campbell et al. 1972). Subsequent studies from this group evaluated the effects of haloperidol on an exclusively autistic sample. In a comparison of haloperidol and two levels of a response-contingent behavioral paradigm in 40 autistic children, the medication conditions yielded significantly more improvement in stereotypy, withdrawal, and word learning than the nonmedication conditions. Behavioral treatment was effective in improving imitative speech and compliance (Campbell et al. 1979). In 1982, Campbell and associates studied a group of 33 subjects treated in a double blind, placebo-controlled crossover design with haloperidol (Campbell et al. 1982a,b). Modest but statistically significant improvement was noted in withdrawal, stereotypy, abnormal object relations, and performance on a discrimination learning task, while hyperactivity improved markedly. Finally, a more recent study of 45 autistics confirmed the behavioral findings, but failed to demonstrate improved performance on discrimination learning (Anderson et al. 1989). A recent secondary analysis of these data indicated that within a cumulative sample of 125 autistic children treated with haloperidol, the fraction of subjects who improved varied from 28 to 84%, depending upon the outcome measure, and a number of patients worsened (Locascio et al. 1991). Between 15 and 34% of subjects improved on placebo, although haloperidol was superior to placebo on all measures. Age and higher IQ predicted better response to haloperidol. Therefore, haloperidol may be relatively less effective in younger autistic children or those with lower IQs.

It should be noted that these studies are probably not appropriate to address the effect of neuroleptics on learning and socialization. Since severely disruptive behavior precludes normal learning and social interaction, a medication that treats the behavioral symptoms will appear to increase learning and socialization. To evaluate a specific effect on the core symptoms of autism, trials must be conducted on high-functioning, nonretarded individuals who exhibit few associated behavioral symptoms.

More recently, open-label trials of risperidone (Fisman and Steele 1996; McDougle et al. 1997; Fisman et al. 1998) and olanzapine (Potenza et al. 1999) in children with PDD suggest that these agents may be empirically used as first-line choice for the treatment of agitation and other common impairing manifestations of autistic disorder, such as overactivity and self-injury (McDougle et al. 1997). They are reviewed in more detail under the section on atypical neuroleptics.

In summary, neuroleptics are not indicated as a primary treatment of autistic disorder. Available clinical trials suggest they may be useful in the treatment of associated behavioral symptoms such as self-injurious behavior, stereotypy, and

hyperactivity. However, the data neither support nor refute an effect upon the core symptoms of autism.

Attention-Deficit Hyperactivity Disorder

Neuroleptics are generally not considered for treatment of ADHD unless standard agents (psychostimulants, antidepressants, and clonidine) either have failed or are contraindicated. As with autistic disorder, case reports in ADHD indicate that antipsychotics may be useful for short-term management of disruptive behavior. Several placebo-controlled studies have reported improvement when neuroleptics were used alone or in combination with stimulants (Greenberg et al. 1972; Gittelman-Klein et al. 1976; Walker et al. 1999). Werry and colleagues (1976) reported that very low doses of haloperidol were comparable to methylphenidate in treating both hyperactivity and attention in ADHD, but that haloperidol produced more unwanted side effects (Werry and Aman 1975). In contrast to psychostimulants, neuroleptics have more often been shown to hamper cognitive performance in hyperactive children (Helper et al. 1963). The positive trials have been criticized on the grounds that they failed to adequately measure cognitive parameters, including attention (Gualtieri and Hicks 1985). In general, the relative success of nonpharmacological treatment, cognitive side effects of antipsychotics, and the liability of long-term risks limit the usefulness of and interest in treating ADHD with neuroleptics.

Personality Disorders

Due to the lack of available studies and diagnostic uncertainty regarding severe personality disorders in children, a clinical description of this diverse class of diagnoses will not be included here. However, the benefit of neuroleptics in the treatment of severe character pathology in adults, especially borderline personality disorder, has long been recognized (Brinkley et al. 1979) and subjected to stringent clinical trials (Soloff et al. 1986, 1989). Although there is mounting evidence that BPD exists in children and adolescents (Petti and Vela 1990), there are no controlled trials of neuroleptics in this population and their use is not currently recommended.

Nonspecific Behavioral Problems

Behavioral disorders comprise the bulk of child psychiatric referrals. Neuroleptics have been used in the treatment of those behaviors that are seen as dangerous or severely disruptive to the child's development and have failed to respond to behavioral or other pharmacological measures.

Self-injurious behavior (SIB) is a common problem in mental retardation, pervasive developmental disorder, Lesch-Nyhan syndrome, and other genetic

syndromes. It has been estimated that 10% of institutionalized mentally retarded individuals exhibit such behavior (Schroeder et al. 1978). Self-injurious behavior was also one of the first clinical indications for neuroleptics, with controlled trials dating back to 1958 (Adamson et al. 1958). Pharmacological intervention should be considered when the behavior is chronic, is severe enough to produce injury, and has failed behavioral treatment and other pharmacological trials (anticonvulsants) (King et al. 1997). Common manifestations include head banging, biting, scratching, picking, and self-mutilation. Severe cases have resulted in subdural hematoma, detached retina, fracture, infection, deformity, and even death (Schroeder et al. 1978; Farber 1987).

Severe aggression is likewise associated with many child psychiatric diagnoses, particularly severe developmental disorders, conduct disorder, and ADHD. Pharmacological treatment alone is rarely sufficient but may be used in a limited fashion to augment a broader treatment program (Stewart et al. 1990). Neuroleptics have been shown to be helpful in aggression appearing specifically in conduct disorder (Campbell et al. 1984; Wells et al. 1991), in ADHD (Alderton and Hodinott 1964), and in mixed diagnostic groups (Cunningham et al. 1968; Cambell et al. 1972) Several agents have FDA approval for severe behavioral disruption in children (Table 3).

Nonspecific agitation often encountered in severely retarded children, anxiety disorders, and situational reactions has resulted in the use of sedating neuroleptics on a short-term basis. Specific behavior may include restlessness, pacing, verbal disruption, or property destruction. Several agents are approved for episodes of severe agitation, subsumed under the terms "severe behavioral disruption" and "nonpsychotic anxiety" (Table 3). However, neuroleptics may produce side effects (akathisia), which exacerbate the symptoms.

Especially in institutionalized children and adults, chronic prescription of neuroleptics without clear diagnostic indications has been deemed an epidemic problem in mental health care, accounting for 30–55% of neuroleptic prescriptions in reporting institutions (Werry et al. 1976; Huges 1977; Linaker 1990). There is some evidence that such use is declining (Reardon et al. 1989; Keck et al. 2001). The current availability of diagnostically specific treatments, the sequelae of chronic neuroleptic exposure, and the existence of alternative agents with superior benefit-to-risk profiles (such as alpha 2-agonists) render the long-term use of neuroleptics as a nonspecific behavioral sedative inappropriate.

Uses In Pediatric Medicine

Nausea and vomiting is ameliorated by low-potency neuroleptics, especially the phenothiazines. Seven neuroleptics are approved for this use, not all of which are approved for psychiatric indications (Table 4). The most appropriate indication for neuroleptics as antiemetic agents is in the treatment of severely medically

ill children, such as cancer patients undergoing chemotherapy, when vomiting places them at serious risk. Their use for emesis during pregnancy should be limited due to potential damage to the fetus, although specific malformations and substantially increased risk with in utero exposure have not been demonstrated (see Contraindications). It should be noted that several of the cases reports of severe dystonia or neuroleptic malignant syndrome have been reported after brief exposure to antiemetics (Klein et al. 1985; Thacker et al. 1990).

Sedation prior to surgery or office procedures is a common, but controversial indication for neuroleptics. In particular, the “DPT” cocktail, an injected combination of the narcotic analgesic, Demerol™ (meperidine) and the phenothiazines Phenergan™ (promethazine) and Thorazine™ (chlorpromazine), has come under criticism. This combination is used in children’s emergency rooms and clinics for surgical and orthopedic procedures and has been associated with the full spectrum of neuroleptic side effects (Snodgrass and Dodge 1989). If neuroleptics must be used, close monitoring for dystonia, akathisia, and extra-pyramidal symptoms (EPS) are necessary. Alternate means of sedation are vastly preferable.

Intractable hiccups and motion sickness are infrequent applications for which some neuroleptics (i.e., prochlorperazine, Compazine™) have been approved. They can only be recommended in children after standard antihistamine antiemetics (i.e., dimenhydrinate, Dramamine™) have failed to have a therapeutic effect.

Contraindications

Absolute contraindications for neuroleptics include hypersensitivity to the agent, acute agranulocytosis, and current episodes of neuroleptic malignant syndrome (Table 5). However, probable contraindications include comatose or obtunded patients, patients who have received high doses of CNS depressants (such as narcotics or barbiturates), patients with a history of blood dyscrasias or bone marrow suppression (especially if related to neuroleptic use), and the presence of subcortical brain injury with temperature dysregulation (Table 5). Relative contraindications include pregnancy and previous neuroleptic malignant syndrome, both of which bear further discussion (Table 5).

Past Episode of Neuroleptic Malignant Syndrome

This rare, potentially fatal reaction to dopamine antagonists is described below (see Adverse Reactions). When a nonpsychotic patient has a history of neuroleptic malignant syndrome (NMS), new treatment with antipsychotic agents is contraindicated. However, many victims of NMS require continuation of treatment for chronic psychosis. Studies in schizophrenic adults suggest that the risk of recurrent NMS upon restarting neuroleptic therapy may be lower than predicted.

TABLE 5 Contraindications to Neuroleptic Therapy

Definite	
	Hypersensitivity to neuroleptics
	Agranulocytosis associated with neuroleptics
	Neuroleptic malignant syndrome (acute)
Probable	
	Comatose or obtunded patients
	Patients receiving high dose CNS depressants
	Pre-existing bone marrow suppression
	Subcortical temperature
Relative	
	History of neuroleptic malignant syndrome
	Pregnancy

Addonizio and colleagues (1987) reviewed 115 cases and found that the authors reported reinstitution of therapy in 26 cases, 10 of which had recurrence of NMS. Pelonero and associates (1985) reviewed NMS cases in which neuroleptics were reinstated and recommended that an agent from a different chemical class should be chosen, of lower potency, and at the lowest possible dose. Both authors recommended intensive monitoring for fever and laboratory markers of NMS with rechallenge. However, retrospective reviews of NMS recurrence are confounded by trends in clinical practice over the past two decades, most significantly that maintenance doses are lower now than in the past, and that atypical neuroleptics have replaced the classical neuroleptics as first-line agents. Recently, Rosebush and Stewart (1989) successfully reinitiated neuroleptic therapy in 13 of 15 cases of NMS with no apparent relationship to neuroleptic dose or potency. Similarly, Pope and colleagues (1991) rechallenged 11 of 20 consecutive cases of NMS and found no recurrences of NMS even with long-term neuroleptic treatment. However, the risk of recurrent NMS following treatment with typical or atypical neuroleptics has not been assessed in children. Rechallenge should be attempted only when neuroleptic therapy is clearly necessary and alternative treatments have failed. On the contrary, with the exception of risperidone in doses above 6 mg/day, atypical neuroleptics appear to have a more benign NMS profile (Tammings et al. 1996).

Pregnancy

Animal studies have shown an increase in congenital anomalies, decrease in viability, and abnormal neuronal growth with prolonged, high dose, exposure to antipsychotic agents in utero (Elia et al. 1987). However, human studies consist

largely of normal populations who received short term, low dose neuroleptics for emesis. Therefore, it is difficult to differentiate the risk of neuroleptic exposure from that of the multiple causes of severe emesis. In these populations there have been reports of slightly increased, but statistically insignificant, risk of birth defects, especially for exposure during the first trimester (Edlund and Craig 1984). Interestingly, one of the few controlled studies found that a retrospective cohort of children exposed to neuroleptics for at least two months in utero had significantly *increased* height and weight compared to controls (Platt et al. 1988).

A French survey found no increased risk of malformation in children of schizophrenic mothers who were exposed to neuroleptics in utero (Godet and Marie-Cardine 1991). Therefore, although psychotropic medication should be avoided in pregnancy when possible, current experience does not indicate a significantly higher risk of birth defects at therapeutic doses of conventional antipsychotics. Their use may be warranted when the symptoms of psychosis are judged to be a health risk to mother and fetus. Prospective studies on the effects of fetal and perinatal exposure to the atypical antipsychotics are required before the safety of these agents is established (Van Tol et al. 1992).

Typical Neuroleptics: Side Effects and Adverse Reactions

The term “neuroleptic” literally means “agent which causes neurologic dysfunction.” As such, it highlights the potential toxicity of this category of medication and the reason for controversy surrounding use of these agents in children. Side effects and adverse reactions to neuroleptics are shown in Table 6.

TABLE 6 Side effects and Adverse Reactions to Neuroleptics

Short term	Long term	Idiosyncratic
Extra-pyramidal symptoms	Tardive dyskinesia	Neuroleptic malignant syndrome
Acute dystonia	Hyperprolactinemia	Agranulocytosis
Cardiac arrhythmias	Hepatic toxicity	Sudden death
Anticholinergic symptoms	Ocular pigmentation	
Akathisia		
Sedation		
Affective blunting		
Cognitive dulling		
Social withdrawal		

Anticholinergic Effects

Anticholinergic side effects are those common to atropine-like agents, including blurred vision, exacerbation of narrow-angle glaucoma, constipation, agitation, and delirium. Table 1 indicates the relative anticholinergic potency of common antipsychotic agents, as well as their affinity for other neuroreceptors. Highly anticholinergic agents should be avoided when these side effects are of concern, such as in the presence of delirium, other anticholinergic agents (antidepressants), glaucoma, encopresis, or neurological illness in which the level of consciousness must be monitored.

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are common effects of antipsychotic therapy, and their severity is proportional to the degree of dopaminergic blockade. The usual presentation is of a parkinsonian-like syndrome comprised of muscular rigidity with or without cogwheeling, tremor, bradykinesia, masked facies, shuffling or festinating gait, and drooling. These effects are most common with high-potency neuroleptics possessing little or no anticholinergic and antihistaminic properties, but can be produced with higher doses of low-potency agents.

The proposed mechanism of EPS is interruption of inhibitory dopaminergic input to the caudate nucleus by D₂ receptor blockers. As discussed above in Chemical Properties, the severity of EPS is most closely correlated with the percent of D₂ receptor blockade and is greatly reduced with clozapine. When dopaminergic inhibition of the caudate is interrupted, the net effects are increased excitatory cholinergic activity in the caudate and parkinsonian abnormalities of movement (Kaufman 1990). The two main pharmacological approaches to treating EPS are based on this mechanism: anticholinergic agents, which reduce cholinergic activity in the caudate, and dopaminergic agonists, which increase nigrostriatal inhibition of the caudate.

Anticholinergic drugs used to treat EPS include both specific and nonspecific agents, many with significant antihistaminic activity as well. These include benztropine (CogentinTM, TreminTM), biperiden (AkinetonTM), and trihexyphenidyl (ArtaneTM). Diphenhydramine (BenadrylTM) is primarily antihistaminic, but has significant anticholinergic activity and is more sedating than the agents noted above. Specific treatment guidelines are given below.

Dopamine agonists (L-dopa, bromocriptine, and amantadine) have been used in adults to treat EPS by enhancing dopamine transmission in the nigrostriatal tract. As one might predict, a significant side effect of this approach is increased psychosis, mania, or agitation. Most adults appear to tolerate the cautious use of dopamine agonists and often report fewer unpleasant side effects than with anticholinergics. Of note, L-dopa has been ineffective in open trials and may have a higher incidence of side effects (Hardie and Lees 1988).

Although amantadine has been used as an antiviral agent in children, its safety profile has not been clearly established (Borison and Davis 1983). One single-blind crossover trial exists comparing amantadine to benztropine for the treatment of EPS in children with Tourette's syndrome (Borison and Davis 1983). Of seven patients, six developed akathisia, four experienced dystonic reactions, and four developed Parkinsonian symptoms upon treatment with haloperidol. Amantadine and benztropine were equally effective at reducing parkinsonian symptoms, but amantadine appeared to be superior against dystonia and akathisia (Borison and Davis 1983). Despite this finding, dopamine agonists must be considered an experimental treatment for EPS in children and adolescents until safety and efficacy are more firmly established.

Acute Dystonia

Dystonia is also more common with high-potency agents. This effect is characterized by the sudden development of cramping and pain, usually involving head, neck, and back musculature. It can be severe enough to compromise respiration or cause skeletal injury. Oculogyric or opisthotonic crises may occur and, untreated, can be life-threatening. Subacute cases may present with dysarthria, jaw or tongue cramping, or dysphagia.

Treatment of dystonic reactions is based on rapid introduction of antiparkinsonian agents. Intramuscular (IM) or intravenous (IV) injection of diphenhydramine (50 mg) or benztropine (2 mg) is often sufficient for large children and adolescents, although intermittent dosing may be necessary. Initial doses may be reduced for smaller children, although dystonic reactions are less common in preadolescents (Campbell 1985). If dystonia fails to resolve within 15–20 minutes after the first injection, the dose is repeated, followed by either a third dose or augmentation with a rapid-acting benzodiazepine (lorazepam 1 mg IM or IV), if needed. Long-term management includes decrease or discontinuation of the antipsychotic agent, changing to a lower-potency agent, or addition of regular doses of antiparkinsonian agents (Table 7). As noted above, recurrent dystonia may respond to amantadine.

Akathisia

Akathisia is the frequent subjective complaint of a need for constant movement. This may or may not be observed on exam as restlessness, agitation, or motoric hyperactivity. In fact, although exceedingly unpleasant for patients, it may yield no observable change in behavior and may be indistinguishable from anxiety. The mechanism underlying this side effect of antipsychotics is unknown but is thought to be mediated by extrapyramidal D₂ blockade and is reduced or absent with agents that show low D₂ occupancy (clozapine). Again, decreasing the antipsychotic dose may be effective. Antiparkinsonian agents may provide some relief but are often less effective at reducing akathisia than parkinsonian EPS. In

TABLE 7 Acute Management of Adverse Reactions

Reaction	Management ^a
Anticholinergic symptoms	Decrease dose Eliminate concurrent anti-Ach drugs Change to higher potency agent
Extrapyramidal symptoms	Decrease dose Add antiparkinsonian agent (e.g., benztropine or biperiden)
Acute dystonia	Airway management Diphenhydramine 50mg IM or IV —or— Benztropine 2 mg IM (may repeat dose q15–20 min) Lorazepam 1–2 mg IM or IV
Akathisia	Decrease dose Antiparkinsonian agents may be ineffective Propranolol 10–30 mg TID —or— Clonazepam 0.5–1.0 mg BID
Neuroleptic malignant syndrome	Discontinue neuroleptics Cardiorespiratory support Hydration May use bromocriptine 2.5–10 mg TID —or— Dantrolene 1–3 mg/ky/day, divided Benzodiazepines may alleviate agitation and rigidity
Hyperprolactinemia	Reduce or discontinue medication Amantadine 100–300 mg/day, divided, may be effective

^a Doses and safety of pharmacologic approaches are not established in preadolescents.

adults, β -adrenergic blocking agents are best studied and appear to be the current medication of choice for neuroleptic-induced akathisia. Propranolol, a nonselective, lipophilic β -adrenergic antagonist, has been used most widely at doses of 20–40 mg TID. However, selective β -1 (betaxolol and metoprolol) and β -2 (ICI) (Kramer 1978) antagonists have been equally effective in double-blind trials (Adler et al. 1989; Kim et al. 1989; Dumon et al. 1992). Interestingly, nadolol, a nonlipophilic β -blocker, appears to be ineffective at reducing akathisia, suggesting that central rather than peripheral β -adrenergic receptor blockade is required (Weizman et al. 1984). Whether β -adrenergic agents are safe or effective

for children with akathisia remains unclear, and safety must be better demonstrated before this approach can be recommended.

Trials of benzodiazepines suggest that these agents may be equal in efficacy, but controlled and long-term studies are few. Both diazepam (Donlan 1973) and clonazepam (Kutcher et al. 1989) have been shown to be beneficial for adults with akathisia, but neither has been compared to propranolol in a controlled fashion.

Clonidine has been tried for akathisia with mixed results and is untested in children for this indication.

Movement Disorders

Abnormal involuntary movements constitute the most common long-term side effect of neuroleptic use, but may also be seen with other medications and disorders (Table 8). There are several manifestations, most involving involuntary, often unconscious, movements of the tongue, face, and neck. Muscle groups with dense motor innervation are most severely affected, so that dyskinesia of hands and feet are next most common, to those of tongue and face followed by limb

TABLE 8 Nonneuroleptic Causes of Tardive Dyskinesia

Medications
L-Dopa
Amphetamines
Anticholinergics
Antidepressants
Lithium
Phenytoin
Psychiatric conditions
Stereotypes of schizophrenia or autism
Spontaneous oral dyskinesia of old age or senility
Oral dyskinesias secondary to dentures or dental conditions
Idiopathic torsion dystonia
Tourette's syndrome and simple tics
Medical/neurological conditions
Wilson's disease
Huntington's disease
Fahr's syndrome
Postanoxic and encephalitic EPS
Sydenham's chorea
CNS manifestation of systemic metabolic disorder
CNS neoplasm

Source: Task Force 1980.

and trunk movements. Specific movements may appear choreoathetoid, tic-like, or even mimicking voluntary habits.

Movements that appear after lowering or discontinuing medication are termed “withdrawal dyskinesia,” while those that appear during chronic administration are called “tardive dyskinesia.” The latter manifestation is rare in patients exposed to neuroleptic treatment for less than 6 months. Although long thought to be irreversible, there are cases of tardive dyskinesia resolving over time or with dopamine agonist treatment (L-dopa or amantadine) (Ankenman 1989; Ludatscher 1989). There are reports of dyskinesia appearing after as little as one dose of a low-potency neuroleptic. However, in general, risk increases with age of the patient (particularly over 50 years), length of exposure, and potency of dopamine blockade.

Since there is no proven treatment for neuroleptic-induced dyskinesia, proper management involves thorough pretreatment counseling, minimization of neuroleptic dose and exposure, and periodic standardized examination for involuntary movements. The Abnormal Involuntary Movement Scale (AIMS) is useful for this purpose (NIH 1985).

Neuroleptic Malignant Syndrome

NMS is a potentially life-threatening adverse reaction to neuroleptics characterized by hyperthermia, “lead pipe” muscular rigidity, altered mental status, hyper- or hypotension, tachycardia, diaphoresis, and pallor. Laboratory findings include myoglobinuria and elevated white blood cell count, muscle and hepatic enzymes. The clinical picture may be mistaken for psychosis, catatonia, EPS, infection, or fever of unknown origin (Harpe and Stoudemire 1987). Levenson (1985) has suggested diagnostic criteria for NMS. In a review of 53 cases, he found fever, rigidity, and elevated creatinine phosphokinase (CPK) to be major manifestations and tachycardia, labile hypertension, tachypnea, altered consciousness, diaphoresis, and leukocytosis to be minor manifestations. The presence of all three major, or two major plus four minor, manifestations is diagnostic of NMS if the clinical history supports this (Levenson 1985). Adityanjee (1992) has cautioned against overdependence on CPK levels to diagnose NMS, since mild elevations in CPK are common in agitated patients, in those receiving intramuscular injections, and in active children. Therefore, levels below 1000 U/L may not be a manifestation of NMS (Adityanjee 1992). Specific diagnostic criteria are still debated, but most descriptions emphasize the presence of four main features: fever, muscular rigidity, altered level of consciousness, and autonomic dysregulation (Nierenberg et al. 1991). Although specific risk factors are not known, high-potency agents, multiple antipsychotics, and polypharmacy have been implicated. Keck et al. (1989) compared 18 adult cases of NMS to controls and found significantly higher neuroleptic doses, rates of dosage increase, and number of intramuscular doses among cases.

Occurrence rates have been estimated between 0.5 and 1.4%, based on the

number of reported cases and estimates of the number of patients exposed to typical neuroleptics (Rosenberg and Green 1989). However, since cases have been reported for even brief or accidental exposure to neuroleptics (Klein et al. 1985; Moore et al. 1986; Thacker et al. 1990; Brown et al. 1991), the number of patients at risk is probably underestimated in these studies. A number of cases have been reported in children as young as 11 months of age (Numa 1991), although differential risk factors or treatment methods for children are virtually unexplored.

Treatment of mild cases may require only supportive measures and cessation of all antidopaminergic and anticholinergic medication. However, in adults, treatment with the dopamine agonist bromocriptine or the peripheral muscle relaxant dantrolene has been advocated (Rosenberg and Green 1989). Close monitoring of cardiac and renal status is required to avoid arrhythmias and myonecrotic kidney failure, respectively. Fever may reach 41°C or higher, requiring hydration and cooling. Bromocriptine mesylate, at (adult) doses of 2.5–10 mg TID, appears to improve rigidity and mental status through central dopaminergic stimulation, while sodium dantrolene, in four divided doses of 1–3 mg/kg/day, decreases rigidity, tachycardia, and myonecrosis through direct action on musculature. Both agents may be used simultaneously (Guze and Baxter 1985; Levenson 1985; Harpe and Stoudemire 1987). Rosenberg and Green (1989) reviewed available case reports and compared the speed of recovery for patients treated with supportive measures alone to those treated with bromocriptine or dantrolene (Rosenberg and Green 1989). They found that the mean response and recovery times for either pharmacological treatment were significantly shorter than for supportive treatment alone. This observation combined with the low incidence of adverse reactions to dantrolene or bromocriptine strongly supports pharmacological treatment of NMS. Other authors have argued that improvements in supportive care techniques may account for these results (Numa 1991), and one prospective study of 24 cases found no advantage to medication over supportive care alone (Rosenbush and Stewart 1989).

Mortality has been estimated from reviews of adult NMS case reports at 11–22% (Adamson et al. 1958; Levenson 1985; Shalev and Munitz 1986; Shalev et al. 1989). Shalev et al. (1989) reviewed 202 cases of NMS and concluded that mortality has significantly decreased from 25% before 1984 to 11.6% currently, independent of the use of dantrolene or bromocriptine. The strongest predictors of poor outcome in their analysis were myoglobinuria and renal failure. Mortality in the presence of these two factors was estimated at 50%.

Reinstitution of neuroleptics in a patient who has recovered from NMS is discussed under Contraindications.

Weight Gain

Current literature shows that one of the most frequently cited side effects of atypical neuroleptics is weight gain. Weight gain is a side effect that can affect

self-image in children, compliance, and long-term health. Lack of available established treatments for weight gain make this a challenging side effect, as children may continue to gain weight as they develop.

The question of whether risperidone-induced weight gain is associated with steatohepatitis has been preliminary addressed by Szigethy and collaborators (1999), who retrospectively ascertained the rate of liver dysfunction observed during risperidone treatment in 38 youngsters with ages ranging from 5 to 17 years with a variety of psychiatric diagnoses. The mean length of risperidone treatment was 15.2 months at a mean dose of 2.5 mg/day. The investigators found that 37 of the 38 children treated with risperidone had serum transaminase or bilirubin values falling within the normal laboratory ranges. One subject had an alanine aminotransferase (ALT) level of 46 U/L. Further reports may be necessary in order to conclude that steatohepatitis is not associated with risperidone use in children.

Data among adults suggest the weight gain during quetiapine treatment is comparable to the weight gain associated with risperidone and approximately 50% of the weight gain reported with olanzapine and clozapine (Jones et al. 1999).

There are no studies or established guidelines in support of appropriate interventions with children who continue to gain weight on neuroleptics. Dietary measures are of the essence. Case-by-case analysis of the risk/benefit ratio should be attempted, with involvement of a dietitian as needed.

Sudden Death

Several case reports exist describing atypical sudden (Cantu 1989), unexplainable demise during treatment with high-potency (Reilly et al. 2000) and neuroleptics. In particular, haloperidol and droperidol have been associated with death during high, but clinically acceptable, injected doses. The discussion of possible mechanisms and relative risk of this rare reaction are beyond the scope of this chapter.

Other Side Effects

Secondary receptor mechanisms underlie a variety of neuroleptic side effects. Low-potency agents commonly produce postural hypotension and/or syncope, presumably through adrenergic blockade, and may produce quinidine-like effects on cardiac conduction. Cases of heart block and ventricular tachycardia have been reported, especially in overdose. Pimozide and thioridazine are notable for higher incidences of QT prolongation and reports of arrhythmias even at therapeutic doses. Available preclinical and clinical data do not suggest that olanzapine contributes to clinically significant QTc prolongation within the therapeutic dose range (Czekalla et al. 1999). Ziprasidone, the most recent FDA-approved atypical

neuroleptic, has been associated with QTc prolongation and a mean increase in heart compared to adult placebo patients (Kanner 1971).

Agranulocytosis. Reported hematological effects include leukopenia, thrombocytopenia, and lymphopenia. However, the most serious of these is rare, idiosyncratic agranulocytosis. Prior to the introduction of clozapine, agranulocytosis occurred in less than 1:2000 cases of, mainly, phenothiazine use. With clozapine, this adverse effect is of greater concern. However, since implementation of mandatory weekly blood monitoring with clozapine prescription, the mortality rate has dropped substantially. Since January 1991, 68 cases of agranulocytosis with one fatality were reported. The manufacturer continues to require that each treatment center assess hematological and cardiac effects weekly in patients receiving clozapine.

Hyperprolactinemia. Prolonged dopaminergic blockade may produce hyperprolactinemia by interfering with dopamine's role in inhibiting prolactin secretion via tuberoinfundibular projections to the anterior pituitary. Possible clinical effects include galactorrhea (both females and males), amenorrhea, and impotence. Galactorrhea can be socially stigmatizing in young adolescents. Neuroleptic-induced hyperprolactinemia has been successfully treated in adults with dopamine agonists (bromocriptine and amantadine) (Siever 1981; Cohn et al. 1985; Matsuoka et al. 1986), although these agents bear the risk of producing or exacerbating psychosis and mania in some cases (Rego and Giller 1989; Turetz et al. 1997). Dopaminergic agonists have not been tested for neuroleptic-induced side effects in children, and the emergence of endocrine abnormalities should prompt reduction or cessation of neuroleptics whenever possible.

Other adverse effects include increased risk of seizure, hepatic toxicity (especially with chlorpromazine), photosensitivity, and ocular pigmentation.

Overdose

The therapeutic index of most conventional neuroleptics is high with regard to lethal toxicity (AHFS 2001). Severe side effects from dopamine blockade usually ensue and constitute a medical emergency before lethal plasma levels are reached (see Acute Dystonia). With pimozide or thioridazine, cardiac arrhythmias may appear early in the progression of toxic symptoms. Signs and symptoms of toxicity include severe forms of the side effects noted above, CNS and cardiovascular depression, severe hypotension, and respiratory depression. Hypertension has been reported in childhood overdose of haloperidol (AHFS, 2000). Overdose of agents with potent anticholinergic properties may present as delirium.

Treatment of neuroleptic overdose is supportive and symptomatic, as there are no antidotes. Extrapyrimal symptoms and neuroleptic malignant syndrome are treated as described in those sections. Cardiac monitoring and respiratory support are needed. There are few reports of death from overdose of neuroleptics.

Abuse/Dependence

Due to the unpleasant side effects and nonreinforcing primary effects, these medications are not generally abused. Tolerance is not described in the classic sense, although receptor up regulation, decreased tissue sensitivity, and withdrawal syndromes are described. Abrupt withdrawal is most often associated with transient dyskinesia and psychosis. Emergence of psychotic symptoms after withdrawal of long-term neuroleptic is sometimes termed “supersensitivity psychosis” and is thought to be a result of dopamine receptor upregulation and subsequent overstimulation upon removal of the drug.

Available Preparations

For most applications in children and adolescents, antipsychotics are administered orally. Intramuscular preparations are available for conditions in which rapid absorption is desirable (Table 9). Most neuroleptics are highly lipophilic allowing for oil-based depot preparations. This is desirable only in instances when chronic use of high-potency neuroleptics is clearly indicated. Currently, haloperidol ($T_{1/2}$ = approximately 21 days) and fluphenazine ($T_{1/2}$ = 7–10 days) decanoates are available for monthly or twice-monthly injections, respectively.

Conventional Neuroleptics: Initiating and Maintaining Treatment

It is advisable to complete a baseline medical assessment prior to neuroleptic treatment. Antipsychotic agents have been shown to produce abnormalities on EEG, psychometric testing, and neurological exam. Baseline vital signs (i.e., blood pressure, weight), physical examination, and laboratory measures including hepatic enzymes are needed for comparison if abnormalities arise during treatment. If therapy is likely to be long term, an initial CPK and, for low-potency agents, EKG are likewise advisable. Prior to treatment, patients and their parents should be informed of both the risks of side effects and adverse reactions noted above and the risk of nontreatment. A screen for abnormal involuntary movements (AIMS) is usually included in the initial neurological exam to rule out preexisting movement disorders. Although no specific teratogenic effects have been described with these agents, a negative pregnancy test and adequate contraceptive use is preferable (see Contraindications).

Since dystonia, akathisia, and anticholinergic and hematological effects generally appear within the first 2 months of starting or increasing medication, it is advisable to monitor these closely after initiating treatment with antipsychotics. Particularly with long-acting agents, blood levels may require up to 50 days to reach steady state, so that continual adjustment of EPS treatment may be required. Neuroleptic malignant syndrome, dyskinesia, and idiosyncratic agranulocytosis

may appear at any time during therapy. The AIMS exam, a CBC with differential, transaminases, and CPK, should be repeated at 6-month intervals. Electrocardiograms (EKGs) should follow any dose change of pimozide or thioridazine, in particular. Clozapine requires a weekly CBC, blood pressure, and pulse during treatment.

Management of Specific Side Effects

Clinical Practice. Starting and maintenance doses, where established, are listed in Table 3. Clinical trials comparing doses of neuroleptics are even more scarce than those proving their efficacy in children. Maintenance doses are determined on an individual basis by starting at the minimal recommended dose and titrating upward to clinical response or unacceptable side effects. As EPS emerge they may be managed by the addition of antiparkinsonian agents, as described above, but should first prompt a reduction of dose where possible. In adults the incidence of acute dystonia is reduced by prophylactic use of anticholinergic agents (Arana et al. 1988).

Selecting a Specific (Traditional) Agent. Two domains influence the choice of a typical antipsychotic: potency for dopaminergic receptor blockade and potency for anticholinergic side effects (Table 1). In general, the former correlates with antipsychotic potency and the risk of precipitating extrapyramidal side effects, although clozapine is a highly potent antipsychotic that produces minimal EPS. The latter correlates with the risks of hypotension, sedation, peripheral and central anticholinergic effects, as well as the ability of the agent to inhibit its own extrapyramidal side effects. In general, a lower-potency agent is chosen when nonspecific sedation is desired, such as in presurgical sedation, short-term treatment of severe aggression and impulsivity, or agitated psychoses. Higher-potency agents are preferable (in equivalent doses) for schizophrenia, Tourette's syndrome, organic psychoses, and longer-term behavior disorders, due to their milder effect on cognition and socialization.

Schizophrenia. As noted below, there are few controlled trials of neuroleptics in childhood schizophrenia. Today, due to their moderately benign side effect profile, atypical neuroleptics constitute the first-line medications of choice for the treatment of psychosis and schizophrenia in children and adolescents (Kumra et al. 1996, 1998). Starting doses for individual atypical neuroleptics are reviewed below.

Typical agents that have been reported as efficacious for the treatment of schizophrenia include chlorpromazine, loxapine, thioridazine, thiothixene, trifluoperazine, and haloperidol. However, children and adolescents are exceedingly sensitive to the sedative and cognitive dulling effects of neuroleptics. In prior years, high-potency agents were considered first-line therapy (Fish et al. 1969; Realmuto et al. 1984). Haloperidol was started at 0.01–0.05 mg/kg/day in two

TABLE 9 Available Preparations and Average Costs of Neuroleptic Drugs

Compound	Trade name	Nonparenteral preparations	INJ	GEN	Average dose/day (mg)	Average cost/day
Chlorpromazine	Thorazine™	Liq: 30, 100 mg/ml Tab: 10, 25, 50, 100, 200 Sup: 25, 100	Yes	No	200	\$1.38
Thioridazine	Mellaril™	Sr: 30, 75, 150, 200 Liq: 25, 30, 100 mg/ml	Yes	Yes	200	\$1.00 (\$0.21)
Mesoridazine	Serentil™	Tab: 10, 15, 25, 50, 100, 150, 200 Liq: 25 mg/mL	Yes	No	100	\$1.33
Trifluoperazine	Stelazine™	Tab: 10, 25, 50, 100	Yes	No	10	\$1.93
Fluphenazine	Prolixin™	Tab: 1, 2, 5, 10 Liq: 5 mg/mL	Yes	No	5	\$2.26
Perphenazine	Trilafon™	Tab: 1, 2.5, 5, 10 Tab: 2, 4, 8, 16	Yes	No	16	\$1.68
Prochlorperazine	Compazine™	Liq: 1 mg/mL Tab: 5, 10, 25 Sup: 2.5, 5, 25 SR: 10, 15, 30	Yes	No	50	\$1.93

Antipsychotic Agents

Chlorprothixene	Taractan™	Tab: 10, 25, 50, 100	Yes	No	100	\$1.37
Thiothixene	Navane™	Liq: 5 mg/mL Cap: 1, 2, 5, 10, 20	Yes	Yes	20	\$1.96 (\$0.50)
Molindone	Moban™	Liq: 20 mg/mL Tab: 5, 10, 25, 50, 100	No	No	100	\$2.51
Pimozide	Orap™	Tab: 2	No	No	2 ^a	\$0.60
Haloperidol	Haldol™	Liq: 2 mg/mL Tab: 0.5, 1, 2, 5, 10, 20	Yes	Yes	6 ^b	\$2.17 (\$0.09)
Droperidol	Inapsine™	Inj: 2.5 mg/mL	No	No	2.5 ^c	Not Available
Loxapine	Loxitane™	Liq: 25 mg/mL Cap: 5, 10, 25, 50	Yes	Yes	50	\$2.94 (\$1.56)
Clozapine	Clozaril™	Tab: 25, 100	No	No	300 ^b	\$10.26
Olanzapine	Zyprexa™	Tab: 2.5, 5, 7.5, 10 mg	No	No	15	\$9.2
Quetiapine	Seroquel™	Tab: 25, 100, 200 mg	No	No	400	\$11.2
Risperidone	Risperdal™	Tab: 0.25, 0.5, 1, 2, 3, 4 mg Liq: 1 mg/mL	No	No	6 mg	\$7.2

For comparison, all average doses are the lowest effective *adult* maintenance dose reported by manufacturer for hospitalized psychotic patients. Cost is based on BID dosing (unless otherwise indicated) at the average wholesale price and availability reported by Medi-Span for June 1992. Cost of generic equivalent given in parentheses, where applicable.

^a For Tourette's syndrome—not approved for psychosis.

^b Based on TID dosing.

^c For sedation—not approved for psychiatric indications.

or three divided doses in small children, or 0.5 mg QHS in older children and adolescents. Although the manufacturer does not declare a maximum dose, maintenance doses above 10–15 mg/day are usually prohibited by side effects and add little to clinical response. If clinical response is not achieved within this range after 2 weeks of uninterrupted therapy with conventional neuroleptics, consideration should be given to augmentation with lithium, anticonvulsants, or benzodiazepines.

Tourette's Syndrome. Haloperidol is initiated in the same manner as for schizophrenic children. However, maintenance doses are much lower. The recommended range is 0.05–0.075 mg/kg/day or up to 3 mg/day, although doses as high as 10 mg/day are occasionally necessary (Kerbeshian and Burd 1988). Since the smallest available haloperidol tablet is 0.5 mg, these may be cut to allow for 0.25 mg increments.

Pimozide is available in 2 mg tablets, which may also be cut to allow for smaller dose increments. The dose is then titrated to 0.2 mg/kg/day or 10 mg/day (whichever is smaller). QT prolongation is evident on EKG at higher doses, and sudden death has occurred at doses above 20 mg/day. Therefore, serial EKGs must be performed during dose titration, and periodic follow-up EKGs are recommended during maintenance therapy.

Pervasive Developmental Disorder and Behavioral Disorders. Since there are no studies demonstrating that neuroleptics relieve the core symptoms of autism, this is not a first-line treatment. Therefore, before using neuroleptics in these disorders, the practitioner must counsel the patient and family on both the realistic benefits to be gained from neuroleptic therapy and the potentially severe liability. Clear clinical guidelines are not available for any behavioral indication, but the best data come from studies of behaviorally disturbed autistic children.

Perry and associates (1989), showed that haloperidol (0.25–4.0 mg/day) was beneficial in irritable, oppositional, autistic children, and that cumulative neuroleptic exposure could be limited by a discontinuous administration schedule without decreasing overall response. Therefore, intermittent treatment may be sufficient and prudent. Campbell and colleagues (1982) have reported success with 0.5–3.0 mg/day (0.02–0.23 mg/kg/day) of haloperidol. Pimozide has been effective in a range of 1–9 mg/day (Naruse et al. 1982).

Monitoring for neuroleptic-associated movement disorders is particularly important in this population, as it may be difficult to distinguish drug side effects from the stereotypies of autism (Campbell et al. 1990).

Treatment guidelines for atypical neuroleptics are discussed below.

How to Withdraw Typical Agents

Withdrawal symptoms associated with abrupt cessation of long-term neuroleptic use include cholinergic rebound (nausea, vomiting, diaphoresis, restlessness, in-

somnia), withdrawal dyskinesia (including oral dyskinesia, ataxia, or choreiform movements), and psychosis (Gardos et al. 1978). The latter is rarely, if ever, seen in patients who did not have psychosis prior to neuroleptic treatment, but it has been suggested that withdrawal of neuroleptics in schizophrenic patients may induce a “supersensitivity psychosis,” which differs from simple relapse (Chouinard and Jones 1980).

Prior to lowering or discontinuing neuroleptic dosage, the patient and family must be cautioned about the possibility of withdrawal symptoms. Withdrawal of the drug should be gradual if treatment has been lengthy or a low-potency agent was used. Close follow-up is needed to monitor for signs of relapse or withdrawal.

ATYPICAL ANTIPSYCHOTIC AGENTS

There are currently five FDA-approved atypical antipsychotic agents in the United States: clozapine, quetiapine, olanzapine, risperidone, and ziprasidone (Buchanan et al. 1998). Their general mechanism of action is illustrated pictorially in Shiloh et al. (1999). Atypical neuroleptics predominantly block serotonin 5-HT_{2A} receptors in the ventral tegmental area, substantia nigra, limbic regions, basal ganglia, and prefrontal cortex. The involvement of 5-HT neural circuits in the mechanism of action of atypical neuroleptics has been partly postulated because 5-HT is known to exert a regulatory action on dopamine (DA) neurons (Stahl 1999). Serotonin may inhibit DA release from striatal nerve terminal, leading to the hypothesis that presynaptic blockade of 5-HT_{2A} receptors may decrease the inhibition of DA activity produced by chronic neuroleptics, functionally increasing dopaminergic activity in certain cerebral regions (Stahl 1999). Atypical antipsychotic agents also antagonize DA D₂ receptors in the mesolimbic region.

Stimulated by new drug developments, numerous case series and case reports of children treated with atypical neuroleptics have appeared in the literature. Table 10 summarizes the majority of clinical trials of atypical neuroleptics conducted in children at the time of this writing. Studies with fewer than 10 subjects have not been included, except for quetiapine and olanzapine. Case reports are not covered in any detail in this chapter. Instead, controlled data and significant open studies of atypical neuroleptics will be discussed in the following sections. (For critical reviews of atypical neuroleptics in children and adolescents, refer to articles by Findling et al. 1996, Masi 1997, Scahill and Lynch 1998, Toren et al. 1998, and Campbell et al. 1999.)

Clozapine (Clozaril™)

Pharmacology

Clozapine is an antipsychotic agent shown to have superior efficacy over traditional neuroleptics in the treatment of (adult) schizophrenia (Kane et al. 1988). Its

TABLE 10 Open and Randomized Controlled Trials of Atypical Antipsychotics in Children and Adolescents

Medication	Indication	Author, year	Study	N	Mean age	Mean/dose range (mg/d)	Results; common side effects
Risperidone	Conduct Disorder	Findling, 2000	RCT	10	10.7	3 mg/kg/d	Superior to placebo in decreased aggression; weight gain
Risperidone	Bipolar Disorder	Frazier, 1999	Ch R	28	10.4	1.7	23/28 improved mania and aggression; weight gain, sedation common
Risperidone	"Disruptive"	Kewley, 1999	CS	36	6–21	.5–6	25/30 had decreased disruptive behavior; weight gain
Risperidone	Mood Disorder/Aggressive	Schreier, 1998	CS	11	9.8	0.75–2.5	8/11 (76%) moderate decreased aggression. 7/8 responders on concurrent mood-stabilizers in sub-therapeutic doses; drowsiness
Risperidone	Autistic Disorder	Nicolson, 1998	Open	10	7–17	1.3	8/10 considered responders; weight gain, sedation
Risperidone	Pervasive Developmental Disorder	McDougle, 1997	Open	18	10.2	1.8	12/18 subjects considered responders by decreased repetitive behavior, aggression and impulsivity; weight gain and sedation
Risperidone	Tourette syndrome	Bruun, 1996	Open	38	8–15	2.7	22/38 (58%) improved(tics); sedation, weight gain, 1 worsened tics
Risperidone	Autistic Disorder	Fisman, 1996	CS	14	9–17	0.75–1.5	Efficacious in 13/14; sedation common
Risperidone	Schizophrenia	Groevich, 1996	Ch R	16	14.9	6	Efficacious in 15/16 patients; sedation in 5/16
Risperidone	Pervasive Developmental Disorder & Mental Retardation	Hardan, 1996	CS	20	8–17	1.5–10	Efficacious adjunct in most patients;

Antipsychotic Agents

Olanzapine	Bipolar Disorder	Frazier, 2000	Open	23	5–14	2.5	Effective for mania or mixed states; weight gain
Olanzapine	Bipolar Disorder	Soutullo, 1999	CS	7	12–17	11	Efficacious adjunct in 5/7 patients
Olanzapine	Schizophrenia	Kumra, 1998	Open	8	15	17.5	Lower BPRS scores for clozapine than for olanzapine
Quetiapine	Autistic Disorder	Martin, 1999	Open	6	10.9	100–350	2/6 improved; 3/6 worsened; weight gain, akathisia
Quetiapine	Bipolar Disorder/ Schizoaffective disorder	McConville, 1999	Open	10	13.1	800	Symptom reduction noted in most patients
Clozapine	Schizophrenia	Turetz, 1997	Open	11	11.3	227	Symptom reduction noted; sedation, EEG changes
Clozapine	Schizophrenia	Kumra, 1996	RCT	10	14.4	176	Superior to haloperidol; seizures and neutropenia
Clozapine	Schizophrenia/ Bipolar Disorder	Kowatch, 1995	CS	10	10	127	Symptom reduction noted with additional medication
Clozapine	Schizophrenia	Frazier, 1994	Open	11	14	370	Symptom reduction noted in most patients
Clozapine	Schizophrenia	Remschmidt, 1994	Ch R	36	18	330	Symptom reduction noted in most patients; 6 d/ced drug
Clozapine	Schizophrenia	Blanz, 1993	CS	57	16.8	285	Symptom reduction noted in most patients; EEG
Clozapine	Schizophrenia	Siefen, 1986	CS	21	18	352	Symptom reduction noted in most patients
Ziprasidone	Tourette's syndrome	Sallee et al, 2000	CS	28	7–17	28.2	Superior to placebo in decreasing tics

RCT: randomized controlled trial; CS: controlled study; Ch R: chart review.

(disputed) efficacy on negative symptoms (Meltzer 1994) has been preliminarily replicated in children and adolescents (Kumra et al. 1996). Clozapine interacts with a wide range of different neurotransmitter receptors, including DA receptors (D4, D1, D2, D3, D5), serotonin receptors type 2 (5-HT_{2A}, 5-HT_{2c}), type 6 (5-HT₆), and type 7 (5-HT₇), α_1 - and α_2 -adrenergic receptors, cholinergic and histaminergic receptors (Charney et al. 1999). Clozapine has shown a much lower DA type-2 receptor occupancy than typical neuroleptics and risperidone and olanzapine (Kapur et al. 1999).

Metabolism and Pharmacokinetics

Kinetic analysis in adults has shown that the T_{max} of 200-mg of oral clozapine is approximately 3 hours, and the elimination half-life is approximately 10 hours (Meltzer 1994). Plasma concentrations show a linear relationship to dosing (Charney et al. 1999). Clozapine is a substrate of the CYP3A, CYP2D6, and the CYP1A2 hepatic cytochrome systems (Flockhart and Oesterheld 2000), therefore, inhibitors or inducers of these systems may have an effect on its metabolism and pharmacokinetics. Clinically relevant drug interactions may occur with clozapine-lorazepam and clozapine-fluvoxamine (Brown et al. 1999). No data are available on the metabolism of clozapine metabolites, norclozapine, and desmethylclozapine in children.

Clinical Trials

Frazier et al. (1994) conducted the first 6-week open clozapine trial (mean daily dose 370 mg) of 11 adolescent with childhood-onset schizophrenia that showed marked improvement in Brief Psychiatric Rating Scale (BPRS) ratings compared to admission drug ratings. This study was followed by a double-blind, parallel-group controlled study of clozapine versus haloperidol in children and adolescents with childhood-onset schizophrenia conducted by Kumra and colleagues at the National Institute of Mental health (NIMH) (Kumra et al. 1996). The investigators randomized 21 patients (mean age, 14.0) with onset of schizophrenia prior to age 12, nonresponsive to typical neuroleptics, to a 6-week double-blind parallel comparison of clozapine (mean final dose, 149 mg/d) or haloperidol, (16 mg/d). Clozapine was superior to haloperidol on all measures of psychosis, as well as negative symptoms. However, hematological abnormalities and seizures often complicated the clinical course, with one third of the group discontinuing the drug due to side effects (Kumra et al. 1996). This finding is both consequential and yet cautioning: close follow-up of potential side effects is warranted when using clozapine in youngsters.

An additional 16-week open study of clozapine involving 11 neuroleptic-resistant children with schizophrenia (mean age 13 years) showed an overall significant symptom reduction, especially positive symptoms. The mean clozapine dosage was 227.3 mg/day. Noticeably, most of the improvement occurred during

the first 6–8 weeks. The major side effects were somnolence and drooling (Turetz et al. 1997).

Side Effect

Clozapine's major drawback is its associated risk for potentially fatal agranulocytosis (Charney et al. 1999). However rare (the cumulative incidence in adults is 0.5–1%), the condition carries a 3–15% associated mortality rate (Alvir et al. 1994). The risk for agranulocytosis is highest during the first trimester of treatment and declines steadily thereafter (Alvir et al. 1994). Acute motor side effects, parkinsonism (Charney et al. 1999), akathisia (Miller et al. 1998), and tardive dyskinesia (Bassitt and Louza Neto 1998) with clozapine are low. Phenomenological overlap between negative symptoms and neuroleptic-induced parkinsonism makes this category difficult to assess (Kane et al. 1994), both in adults and in adolescents. In addition, clozapine can induce seizures, increased heart rate, arrhythmias, and weight gain (Miller et al. 1998). Sedation and excessive salivation are less worrisome potential side effects. The overall risk-benefit ratio should determine the ultimate indication for this drug in the treatment of neuroleptic-resistant youngsters.

Clinical Practice

Clozapine is not FDA approved for patients younger than age 16. In adults the initial dose is 12.5 mg 1–2 times daily, increased by 25–50 mg/day to a maximum of 300–450 mg/day in divided doses by the end of 2 weeks (AHFS 2001). Children are usually intolerant of rapid titration schedules. Gradual reduction over 1–2 weeks is recommended for discontinuation of clozapine, except in cases warranted by medical conditions. Patients on clozapine are required to receive weekly blood counts throughout the first 6 months of therapy and biweekly counts thereafter.

Quetiapine (Seroquel™)

Pharmacology

Quetiapine is a dibenzothiazepine-derivative antipsychotic agent (AHFS 2001). Because of pharmacological differences with phenothiazines and butyrophenones, quetiapine is considered an atypical antipsychotic agent. The mechanism of action (not fully elucidated) appears to involve antagonism at serotonin type 1 (5-HT_{1A}), type 2 (5-HT_{2A}, 5-HT_{2c}), and type 6 (5-HT₆) receptors (AHFS 2001). It also binds to D1, D5, D2, D3, and D4 receptors, although quetiapine has a relatively low affinity for DA D2 receptors as measured by PET scans comparing the time course of blockade of DA D2 and serotonin 5-HT₂ receptors (Gefvert et al. 1998). Compared to clozapine, quetiapine has much the same ratio of D2/5-HT₂ occupancy (Gefvert et al. 1998), a low affinity for α_1 - and α_2 -adrenergic

receptors (Saller and Salama 1993), and lack of dorsal striatum c-fos activation (Turney et al. 1984).

Metabolism and Pharmacokinetics

The acute kinetics of quetiapine are linear up to a dose of 600 mg/day (Davis et al. 1999). The elimination half-life ($T_{\beta 1/2}$) in adults is approximately 6 hours. Quetiapine is a substrate of the CYP3A and the CYP1A2 cytochrome systems, therefore it may be affected by CYP3A and CYP1A2 inhibitors (such as fluvoxamine) (Flockhart and Oesterheld 2000). Drug clearance may be reduced in elderly patients with schizophrenia (Gefert et al. 1998). Presently, comparable data on pediatric populations are not available.

Clinical Trials

Two recent quetiapine pediatric reports show contradictory results, perhaps due in part to the difference in target populations studied. In a recent 16-week, quetiapine open-label trial of six male children and adolescents with autistic disorder and mental retardation (mean age of 10.9 years), no statistically significant improvement was ascertained between baseline and endpoint for the group as a whole (Martin et al. 1999). Two (of six) subjects were considered responders based in improved impulsivity after 16 weeks of treatment. Dosages ranged from 100 to 350 mg/day (1.6–5.2 mg/kg/day). Three subjects dropped out prematurely because of lack of response and sedation. Other significant side effects included behavioral activation, increased appetite, and weight gain (range, 0.9–8.2 kg) (Martin et al. 1999).

Conversely, quetiapine was well tolerated and effective in 10 adolescents with chronic or intermittent psychotic disorders (ages 12–15 years). Quetiapine was dosed twice daily starting at 25 mg twice daily and reaching 400 mg twice daily by day 20. The study noted improvement in positive and negative symptoms, as shown by significant decreases from baseline to endpoint in standard rating scales. Of note, no significant differences were observed between 100 mg twice daily and 400 mg twice daily. The most common adverse events were postural tachycardia and insomnia (McConville et al. 2000).

Controlled studies and head-to-head comparisons of quetiapine in children and adolescents are needed in order to establish efficacy and safety in this population.

Side Effects

Clinical trials (Barnes and McPhillips 1998) and case series of elderly hospitalized patients (Madhusoodanan et al. 2000) and youngsters (McConville et al. 2000) treated with quetiapine suggest that quetiapine has a beneficial side effect profile, particularly with regard to extrapyramidal symptoms. Anecdotally, the most frequently reported side effects for quetiapine in adults are sedation and headache, although postural tachycardia, insomnia (McConville et al. 2000), be-

havioral activation, increased appetite, and weight gain (Martin et al. 1999) have been described in adolescents treated with quetiapine.

Clinical Practice

Compared to placebo, quetiapine has demonstrated antipsychotic efficacy in adults at dosages of 150–750 mg/day (Charney et al. 1999). The optimal dose in the treatment of adults with schizophrenia appears to be 300 mg/day (Charney et al. 1999). The range reported in children (Martin et al. 1999) and adolescents (McConville et al. 2000) is wide—100–800 mg/day.

Quetiapine is not approved for persons under 18 years of age. For the management of psychotic disorders, the recommended initial dosage in adults is 25 mg twice daily (AHFS 2001). Dosage may be increased in increments of 25 mg twice daily on the second or third day as tolerated to a target dose of 300–400 mg daily in two or three divided doses by the fourth day (AHFS 2001). Safety in dosages above 800 mg daily has not been established for adults or children.

Olanzapine (Zyprexa™)

Pharmacology

Olanzapine is a thienobenzodiazepine-derivative antipsychotic agent (AHFS 2001), chemically and pharmacologically similar to clozapine. Olanzapine has shown modest (Conley et al. 1998) to significant (Martin et al. 1997) efficacy in the acute reduction of negative, psychotic, and disorganized symptoms in adults with schizophrenia (Ho et al. 1999). The exact mechanism of antipsychotic action of olanzapine has not been fully elucidated but appears to involve antagonism at serotonin type 2A, 2C, type 3, type 6, and DA receptors (Charney et al. 1999). In vivo and in vitro studies of olanzapine have shown weak antagonism at D2 receptors and a comparatively higher affinity for the D4 receptor (Charney et al. 1999), although higher doses (20 mg) may produce relatively high levels (82.8%) of D2 occupancy rates. The apparently low incidence of extrapyramidal effects associated with olanzapine therapy (Charney et al. 1999) suggests that the drug is more active in the mesolimbic than the neostriatal dopaminergic system (AHFS 2001). With chronic treatment it upregulates D2 receptors in the striatum (Charney et al. 1999). Olanzapine exhibits comparatively weaker α_1 -adrenergic blocking activity that may cause occasional orthostatic hypotension, histaminergic H₁ blockade, which may cause sedation, and muscarinic blockade (Bymaster et al. 1997), which may account for the potential anticholinergic activity. It possesses no affinity for γ -aminobutyric acid (GABA) receptors.

Metabolism and Pharmacokinetics

Olanzapine has a relatively weak affinity for the CYP-2D6, -1A2, -3A4, and -2C19 cytochrome systems (Flockhart and Oesterheld 2000). In adults the T_{max} is 5 hours and the mean plasma elimination half-life (T_{1/2}) is 30 hours (Charney

et al. 1999). Its plasma kinetics suggests linear dose proportionality (AHFS 2001). Female subjects have been reported to have a slower metabolism and higher plasma levels than male subjects (Kelly et al. 1999). Carbamazepine and other inducers of the CY-1A2 system (i.e., cigarette smoking) may induce its metabolism (Flockhart and Oesterheld 2000). Conversely, fluvoxamine and other inhibitors of CY-1A2 (i.e., caffeine, cimetidine) may potentiate it (Flockhart and Oesterheld 2000).

Clinical Trials

Overall negative results were reported in one recent olanzapine study of 8 children with treatment-refractory childhood-onset schizophrenia. Fifteen patients who had received 6-week open-label clozapine trials were used as a comparison group. At week 8, the investigators reported a 17% improvement in the BPRS score, a 27% improvement in negative symptoms, and a 1% improvement in positive symptoms, relative to admission status on typical neuroleptics. The magnitude of the effect sizes for clinical improvement was larger for the clozapine group than for the olanzapine group. In this otherwise negative report, the authors concluded that olanzapine may have efficacy for some children and adolescents with treatment-refractory schizophrenia (Kumra et al. 1998).

Conversely, replicating an adult report (Berk et al. 1999), 23 youngsters with bipolar disorder (ages 5–14 years) showed a response rate (defined as $\geq 30\%$ improvement from baseline to endpoint in Young Mania Rating Scale (YMRS) total score and a CGI Bipolar version—mania score ≤ 3 at endpoint) of 60%, in an 8-week open-label trial of olanzapine (range of 2.5–20 mg/day). Extrapyramidal side effects were not significant, but increases were observed in weight at the end of the study (mean 4.98 kg) (Frazier et al. 1999a).

Likewise, five of seven (71%) manic adolescents (ages 12–17 years) with bipolar disorder showed a marked-to-moderate response to olanzapine open-label treatment at a mean dose of 0.14 mg/kg/day (11 mg/day). The authors concluded that olanzapine may have antimanic effects in some adolescents with acute mania (Soutullo et al. 1999).

Side Effects

Olanzapine extrapyramidal side effects are mild even at relatively high levels of DA D2 occupancy (Raeder et al. 1999). At relatively high olanzapine doses (20–25 mg/d), akathisia has been described (Jausse et al. 1998). Other side effects include weight gain and sedation (Charney et al. 1999). Anticholinergic levels (and anticholinergic side effects) are less than those of clozapine-treated adult patients (Chengappa et al. 2000). Prolactin elevations after short-term exposure to olanzapine have been recently described in seven children and adolescents with early-onset psychosis, suggesting a closer scrutiny of chronic patients receiving olanzapine until a more definitive safety profile of this drug is available in children and adolescents (Wressell et al. 1990).

Thirteen adult cases of severe hypertriglyceridemia (>600 mg/dL) associated with olanzapine and quetiapine treatment have been recently reported (Meyer 1999). Three of these patients also developed new-onset diabetes. Underlying mechanisms for atypical antipsychotic-induced hypertriglyceridemia are unclear, but this report suggests that clinical monitoring of serum lipids may be warranted with acute use of newer antipsychotic agents among youngsters developing significant obesity or glucose abnormalities (Meyer 1999).

Olanzapine should be used with caution with concomitant use of other drugs that lower the seizure threshold (i.e., thioridazine).

Clinical Practice

Olanzapine is available in 2.5g, 5g, 7.5g, and 10 mg tablets. Recently, olanzapine has been approved in an orally disintegrating tablet formulation called Zyprexa (Zydis™) (Lilly). Available in lyophilisate formulation 5, 10, 15, and 20 mg tablets, it is supposed to disintegrate in the mouth within seconds, allowing its content to be swallowed without liquid (AHFS 2001).

Although the recommended starting dose in older adolescents is comparable to adults, i.e., 5–10 mg once daily (AHFS 2001), a starting dose of 2.5 mg at bedtime may be less sedative. The titration in adults can be increased by 5 mg/day at intervals of 1 week to a maximum dose of 20 mg/day (AHFS 2001). The use of olanzapine in preadolescents is not FDA approved, and few guidelines are available through the clinical literature. The starting dose may be (lower than) 2.5 mg/day adjusted by 2.5 mg/day at intervals of 1 week to a maximum dose of 15 mg/day (Findling et al. 1998).

Risperidone (Risperdal™)

Pharmacology

Risperidone is a benzisoxazol derivative with high affinity for the serotonin 5-HT_{2A} and the DA D₂ receptors. It has shown significant improvement on positive and negative in adults (Lindenmayer et al. 1998) and adolescents (Armenteros et al. 1997) with schizophrenia. The in vitro affinity for the 5HT_{2A} receptor is 20 times higher than the D₂ receptor (Charney et al. 1999). Risperidone also has relatively high affinity for H₁ histamine receptors and for α_1 -noradrenergic receptors (AHFS 2001). It increases DA turnover in frontal cortex, but only mildly in striatum (Fink-Jensen and Kristensen 1994). At low doses, risperidone stimulates c-fos synthesis in the nucleus accumbens but not in the striatum (Charney et al. 1999).

Metabolism and Pharmacokinetics

Risperidone is metabolized by the liver isoenzyme CYP-2D6, therefore 2D6 polymorphisms can account for important individual variations in plasma levels (Flockhart and Oesterheld 2000). Concomitant 2D6-metabolized medications

(i.e., serotonin-reuptake inhibitors, tricyclics, psychostimulants, clozapine) may alter drug clearance and plasma concentration of risperidone. Likewise, CYP-2D6 inhibitors (i.e., paroxetine) can elevate risperidone levels (Sproule et al. 1997). The major active metabolite of risperidone, 9-hydroxyrisperidone (90HR), is renally excreted. After a 1 mg dose, the T_{max} for risperidone (in adults) is 1 hour, and 3 hours for 90HR (Charney et al. 1999). The $T_{\beta 1/2}$ for risperidone is approximately 3 hours, and 22 hours for 90HR. Kinetics are dose-proportional up to 10 mg (Charney et al. 1999).

Clinical Trials

Risperidone has been shown to have efficacy in improving positive and negative symptoms in adults with schizophrenia (Chouinard et al. 1993). Reflecting perhaps the lower prevalence of childhood-onset schizophrenia compared to adult-onset schizophrenia (Howard et al. 1993) and/or the high incidence of aggression as a presenting problem among children with neuropsychiatric disorders, a majority of studies of risperidone conducted in youngsters so far has been conducted in disorders involving aggression rather than psychosis. Only two studies of risperidone in children with schizophrenia have been reported in the last 5 years. Conversely, open trials of risperidone for the treatment of aggression in children with autistic disorder (Fisman and Steele 1996; Findling et al. 1997; McDougle et al. 1997; Nicolson et al. 1998), bipolar disorder (Schreier 1998; Frazier et al. 1999b), and mental retardation (Hardan et al. 1996) have appeared in the recent literature.

Similarly, one controlled study of risperidone for the treatment of pediatric aggression has been reported recently (Findling et al. 2000). In it, 20 children (mean age 9.2 years) diagnosed with conduct disorder were randomly assigned to receive placebo or risperidone in a 10-week, double-blind design (Findling et al. 2000). The average dose was 0.028 mg/kg/day. A maximum 3.0 mg daily dose was used in patients weighing more than 50 kg. On intent-to-treat analysis, subjects who received risperidone were significantly less aggressive (not on all outcome measures, i.e., Achenbach) during the last 4 weeks of the study than those who received placebo. Increased appetite and sedation were considered mild and transient, although the mean predicted weight increase for patients on risperidone was 9.3 lb (4.2 kg). As the authors point out, it is uncertain if weight gain will be an important long-term impediment to risperidone therapy in this population (Findling et al. 2000).

The potential use of risperidone in the treatment of pediatric mania has been recently suggested by a retrospective chart review of outpatients with the diagnosis of bipolar disorder treated with risperidone (Frazier et al. 1999). Using a categorical definition of improvement of CGI of ≤ 2 , 28 children (mean age, 10.4) receiving a mean dose of 1.7 mg over an average period of 6.1 months were assessed for mania, psychosis, aggression, and ADHD. Eighty-two percent

(23/28) of the children showed improvement in manic and aggressive symptoms, 69% in psychotic symptoms, and 8% in ADHD symptoms. The average time to optimal response was 1.9 months. This study suggests that risperidone in low doses may be effective in the maintenance treatment of mania in children. The therapeutic effect regarding aggression is, as the authors point out, consistent with the emergent body of literature showing that risperidone, at relatively low doses, may also be effective in the treatment of aggression in children (Frazier et al. 1999). Treatment with risperidone was overall well tolerated, although five patients (18%) had increased weight, and five had sedation. Although the weight gain in adults treated with risperidone can be modest, in children and adolescents this can be a concerning side effect (Brecher and Geller 1997). One child became more aggressive during risperidone treatment, illustrating that occasionally children with mania may become even more activated with risperidone (Frazier et al. 1999b).

Until 1997 no prospective systematic studies of risperidone treatment in children with PDD had been published. Since then, four open-label studies of risperidone have been conducted in children with PDD, making this the most accepted off-label indication for risperidone in children and adolescents. Response rates among children with PDD have ranged from 66% (McDougle et al. 1997) to 92% (Fisman and Steele 1996).

The first 12-week, prospective, open-label monotherapy risperidone trial of 15 boys and 3 girls with PDD (mean age of 10.2 years) included 11 subjects with autistic disorder and 3 with Asperger's disorder. Fourteen subjects had comorbid mental retardation. The optimal dose was 1.8 mg/day. Clinical Global Impression Scale rating at baseline compared with CGI after 12 weeks of risperidone treatment showed that 12 (66%) of 18 subjects (7/11 with autistic disorder, 3/3 with Asperger's) had significant improvement in global treatment response. The most common side effects were weight gain (mean range 17.8 lb.), and sedation (Campbell et al. 1990).

A second open, 12-week prospective trial of risperidone in children with autistic disorder (age range 4.5–10.8 years) showed CGI-rated improvement in 8 of the 10 children. Maximum dosage was 6 mg (0.1 mg/kg) daily. Children gained an average of 3.5 kg over the 12 weeks of the study (Nicholson et al. 1998).

Likewise, in a series of 14 children and adolescents (ages 9–17 years) with PDD, 13 of 14 patients appeared to benefit from acute and maintenance (mean 7 months) risperidone monotherapy treatment on CGI ratings. Optimal dosages ranged from 0.75 to 1.5 mg daily in divided doses (Fisman and Steele 1996).

In a fourth open clinical trial, 20 children and adolescents with mental retardation and PDD (age range 8–17 years), refractory to previous psychotropic treatments, received risperidone dosages ranging from 1 to 4 mg/day in the responders and from 4.5 to 10 mg/day among the nonresponders. A limitation of

this study was the concomitant use of other medications (5 patients on lithium, 4 on carbamazepine, and 3 on valproic acid). Nevertheless, in a follow-up period (8–15 months), risperidone still showed decreased aggression in eleven children. Two patients discontinued the drug due to amenorrhea and vomiting, respectively; two adolescent girls developed galactorrhea; and three patients had marked weight increase (Hardan et al. 1996). Controlled studies are needed to determine risperidone's efficacy and safety in this specific population.

Turgay and colleagues (2001) recently conducted a double-blind, placebo-controlled study of risperidone in children with conduct and oppositional defiant disorders and disruptive behavior not otherwise specified who had suboptimal IQ levels (35–84). One hundred ten children 5–12 years of age were randomized to treatment with placebo or risperidone for 6 weeks. Doses ranged from 0.02 to 0.06 mg/kg every morning (mean dose 0.03 mg/kg/day). Risperidone was found to be superior to placebo in reducing behavioral disturbances after 1 week of treatment and persisted throughout the 6-week trial. Moreover, risperidone was not only more effective than placebo in treating children with severe conduct disturbances and suboptimal IQs but well tolerated with few side effects. Somnolence and sedation were the most common side effects (Turgay et al. 2001). In fact, the authors reported only one patient (of the 110 enrolled) who experienced a “serious” adverse event, and this patient was on placebo.

A 4-week open trial of risperidone involving 38 patients with Tourette's syndrome, refractory to conventional neuroleptics or alpha 2-adrenergic agonist, showed improvement on tic severity measured by the Yale Global Tic Severity Scale (YGTSS) in 22 of 38 (58%) patients, at a mean dose of 2.7 mg/day. Of note, 8 patients discontinued risperidone due to intolerable side effects (Bruun and Budman 1996).

Case History

A 10-year-old boy was admitted to an inpatient facility with increasing agitation, dysphoria, and a history of auditory hallucinations. On relatively high doses of risperidone for 18 months, he had a concurrent history of prior facial tics, noticed to be worsened shortly after admission. He was given a few doses of thioridazine PRN for agitation. The attending physician faced the dilemma of tapering off the atypical agent (i.e., risperidone) considering that the emergent “tics” could reflect emergent symptoms of tardive dyskinesia, or whether to increase the atypical agent, considering that the “recurrence of tics” deserved increased neuroleptic dosage. The onset of tics in the context of medication change or other psychiatric or medical comorbidity illustrates one of the challenges of using [atypical] neuroleptics in children. The potential effects of increased or decreased CNS dopaminergic transmission on tics or dystonic movements (which are often confused with withdrawal dyskinesia) are unknown. Decreasing the medication may

stimulate the emergence of withdrawal dyskinesias, and yet increasing the medication may worsen the symptoms as a consequence of a potential moderate increase of DA release in the basal ganglia. The underlying biological mechanisms and clinical consequence of a potential moderate increase of dopaminergic release in the basal ganglia as a consequence of 5-HT₂ blockade (Stahl 1999) have not been adequately studied in child psychiatry.

The only open pilot study of risperidone in adolescents diagnosed with schizophrenia involved 10 outpatients (range 11–18 years) treated for 6 weeks after a 2-week washout. Significant improvement was ascertained on standard rating scales comparing baseline with endpoint at a mean dose of 6.6 mg/day. Four children developed EPS associated with risperidone use. The authors noted that the relatively high incidence of EPS may have been due to high doses used (4–10 mg) during rapid titration schedules (Armenteros et al. 1997).

A retrospective review using the BPRS and the CGI scale of 16 children and adolescents (mean 14.9 years) diagnosed with psychotic disorders (13 patients with schizophrenia, 2 with schizo-affective disorder, 1 with schizophreniform disorder) found significant improvements at a mean daily dose of 5.9 mg (range 2–10). Five patients developed mild sedation and 3 developed EPS (Grcevich et al. 1996).

Finally, 8 of 11 (73%) refractory outpatient children and adolescents (mean 9.8 years) with concurrent affective symptoms (suggestive of bipolar disorder), aggressive and violent behavior, appeared to have therapeutic responses to low doses of risperidone (0.75–2.5 mg daily) on a naturalistic follow-up. Seven of the 8 responders were taking concurrent medications. One child gained 13 lb (6 kg) during the follow-up (Schreier 1998).

Side Effects

Risperidone has been described as having significant less acute (dystonia, akathisia) and chronic (tardive dyskinesia) extrapyramidal side effects than typical neuroleptics (Simpson and Lindenmayer 1997; Charney et al. 1999). Parkinsonian and anticholinergic side effects in adults are minimized below 6 mg/day, whereas above this daily dose motor side effects may be comparable to haloperidol (Charney et al. 1999). In pediatric clinical series, weight gain and sedation have been the most commonly reported side effects in children and adolescents. Sedation is usually transitory, whereas weight gain may be a deterring factor in the overall treatment.

Clinical Practice

Risperidone is supplied in 0.25g, 0.5g, 1, 2, 3, and four 4 mg tablets and in oral solution, 1 mg/mL (which should not be mixed with cola or tea) (AHFS 2001).

Risperidone is usually started at 0.25 mg daily on day 1 and increased to 0.25 mg BID on day 5 in children below age 12. It can be subsequently increased by 0.25 mg daily every third day to reach a target dose of 3mg BID in cases of acute psychosis (Findling et al. 1998). In adolescents above age 12, the usual initial dose is 0.5 mg BID increased to 1 mg BID on day 3, and subsequently increased by 0.5 mg daily every third day to reach a target dose of 3mg BID in cases of acute psychosis (Findling et al. 1998). The treatment of PDD is usually approached with a lower target dose in mind, close to 2 mg daily for preadolescents and 3 mg daily for adolescents. It may be switched to once-daily dosing after titration. Caution should be exercised when administered with other drugs that may potentially prolong the QT interval, i.e., pimozide (Flockhart et al. 2000). A therapeutic range for serum risperidone has not been established, but 6 mg/day is considered the optimum dose for most patients, achieving serum levels within 50–150 nmol/L. (Olesen et al. 1998).

Ziprasidone (Geodon™)

Pharmacology

Ziprasidone is a benzothiazolylpiperazine atypical antipsychotic agent with combined dopamine and serotonin receptor antagonist activity. Ziprasidone is a potent 5-HT_{2A} and weak DA D2 receptor antagonist. Ziprasidone also has high affinity for the 5-HT_{1A}, 5-HT_{1D}, and 5-HT_{2C} receptor subtypes (AHFS 2001). Sprouse et al. (1999) have suggested that ziprasidone's high (agonist) affinity for 5-HT_{1A} receptors, which differs from both clozapine and olanzapine, may result in anxiolytic or antidepressant action (Sprouse et al 1999).

Metabolism and Pharmacokinetics

Ziprasidone tends to show linear pharmacokinetics. Steady state can be achieved after one day (Miceli et al. 2000). Ziprasidone is highly protein-bound (>99%) and thoroughly metabolized and eliminated via hepatic metabolism (AHFS 2001). Studies indicate that CYP3A4 is the major cytochrome system contributing to ziprasidone's oxidative metabolism (Everson et al. 2000), therefore it is not surprising that carbamazepine, an inducer of the CYP3A4 system, at 200 mg BID for 21 days (AHFS 2001) resulted in a decrease of approximately 35% in ziprasidone plasma concentration area under the curve (AUC) (AHFS 2001). Conversely, ketoconazole, an inhibitor of the CYP3A4 system at 400 mg BID for 5 days, increased ziprasidone's AUC by 35% (AHFS 2001). Ziprasidone has no active metabolites described, and its mean terminal half-life is approximately 7 hours (AHFS 2001).

Clinical Trials

Clinical trials indicate that ziprasidone is effective in treating positive and negative symptoms of schizophrenia (Daniel and Copeland 2000) and affective symp-

toms in schizoaffective disorder (Keck et al. 2001). Daniel and colleagues (2000) reported that both 80 and 160 mg/day were significantly better than placebo at reducing symptoms of schizophrenia (Daniel and Copeland 2000). Similarly, Keck and colleagues (2001) randomized 139 adult patients with schizoaffective disorder to receive ziprasidone 40 mg/day, 120 mg/day, or placebo over 28 days, and found that ziprasidone at 120 and 160 mg/day was significantly more effective than placebo in improving standard rating scales measuring clinical improvement (Keck et al. 2001).

Overall, the safety and efficacy of ziprasidone in pediatric patients with neuropsychiatric disorders have not been established (AHFS 2001). The only published study in pediatric patients is a pilot study by Sallee et al. (2000) comparing ziprasidone against placebo for the treatment of Tourette's syndrome (Sallee et al. 2000). Twenty-eight patients (7–17 years) received ziprasidone or placebo for 56 days, starting at a dose of 5 mg/day to a maximum of 40 mg/day. In this study ziprasidone was significantly more effective than placebo in reducing global measures of clinical severity and tics at a mean of 28.2 mg daily (Sallee et al. 2000). Mild transient somnolence was the most common adverse event (Sallee et al. 2000). Although the authors conclude that ziprasidone may be associated with a lower risk of extrapyramidal side effects in children, a comparison with conventional neuroleptics is warranted.

Side Effects

Ziprasidone is generally well tolerated (Miceli et al. 2000). Concurrent with initial clinical trials (AHFS 2001), the most frequent adverse events associated with ziprasidone in Daniel's study (2000) were nausea/dyspepsia, dizziness, and transient somnolence (Daniel and Copeland 2000), possibly related to alpha blockade and a histaminergic sedative effect, respectively (AHFS 2001). The percentage of patients experiencing adverse events was similar for 80 and 120 mg/day treatment groups (Adityanjee 1992). Of note, in a comparative study, Allison et al. (1999) found that placebo was associated with a mean weight reduction of 0.74 kg, and ziprasidone was associated with a mean weight reduction of 0.04 kg (Allison et al. 1999).

QTc Prolongation

In a study comparing the QTc-prolonging effect of ziprasidone with other neuroleptics in adult normal volunteers (AHFS 2001), the mean increase in QTc from baseline for ziprasidone ranged from 9 to 14 msec greater than haloperidol, quetiapine, olanzapine, and risperidone, but 14 msec less than thioridazine (AHFS 2001). In placebo-controlled trials (AHFS 2001), ziprasidone increased the QTc interval by approximately 10 msec compared to placebo, at the highest recommended dose of 160 mg/day (AHFS 2001).

Because of ziprasidone's described potential prolongation of the QTc interval (AHFS 2001), it should not be given with other drugs that prolong the QTc

interval and that have an association with fatal arrhythmias, like quinidine, pimozide, and thioridazine (AHFS 2001). Certain clinical circumstances (i.e., bradycardia, hypokalemia, and hypomagnesemia) may increase the risk of sudden death in association with the use of drugs that potentially prolong the QTc interval and should be particularly monitored when using ziprasidone (AHFS 2001).

Clinical Practice

Ziprasidone is available in 20, 40, 60, and 80 mg capsules, as well as in 5, 10, and 20 mg intramuscular preparations. An interesting pilot study by Sallee et al. (2000) using ziprasidone for Tourette's syndrome warrants replication. In the meantime, we cannot endorse the use of ziprasidone in children and adolescents until its safety and efficacy in pediatric patients with psychiatric disorders have been well studied.

Summary

Based on preliminary yet accumulating open data and clinical experience, risperidone or olanzapine are recommended as first-line agents for childhood-onset schizophrenia, pediatric psychosis, and clinical aggression, especially in the context of an autistic disorder spectrum. Quetiapine and ziprasidone may be considered in partial responders or if extrapyramidal side effects develop. Ziprasidone may have the added benefit of minimal weight gain compared to other neuroleptics, although this characteristic needs to be further evaluated in daily clinical practice. Clozapine is a second to third-line option with treatment-refractory patients. Dose-dependent extrapyramidal side effects with risperidone, potentially fatal agranulocytosis with clozapine (Brown et al. 1999), and weight gain on any of these agents should be monitored carefully.

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13

Lithium

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Lithium, a natural salt, was discovered in 1817. It has been used to treat various medical conditions for the past 175 years. Initially, lithia salts were used to treat gout, which was believed to include symptoms of depression and mania. After serious toxicity was associated with its widespread use in elixirs and tonics and as a salt substitute, it fell out of favor (Lenox and Manji, 1995; Manji et al., 1999, 2000; Lenox and Hahn, 2000). Lithium was then rediscovered in the 1950s by Cade (1949) for the treatment of both acute bipolar mania and depression, as well as for long-term bipolar disorder prophylaxis (Hirschfeld, 1994; Bowden, 1998). There have been more studies of lithium in the treatment of bipolar children and adolescents than any other mood stabilizer, but the majority of these studies are uncontrolled and in heterogeneous groups of patients. Lithium's only FDA-established indication is for the acute and maintenance treatment of bipolar disorders in patients at least 12 years old. Nonetheless, lithium's usefulness in treating a wide variety of psychiatric disorders in both adolescents and children younger than 12 years of age continues to be actively investigated. The majority of these studies explore lithium's utility in the treatment of child and adolescent

TABLE 1 Pharmacokinetic Properties of Lithium

Absorption	Peak serum levels	Serum half-life	Principle route of excretion
Gastrointestinal	2–4 hours	20–24 hours	Renal

bipolar disorder, augmenting antidepressants in the treatment of depression, and the treatment of aggressive behaviors, including disruptive behavioral and attention-deficit hyperactivity disorders (Youngerman and Canino, 1978; Jefferson, 1982; Fetner and Geller, 1992; Kafantaris, 1995; Geller and Luby, 1997; Kowatch and Bucci, 1998; Ryan et al., 1999).

CHEMICAL PROPERTIES

Lithium carbonate (Li_2CO_3) is a very soluble cation salt that is rapidly absorbed after oral administration by the gastrointestinal tract (Table 1). A citrate form of lithium is also available as a syrup, which contains 8 mEq lithium/5 mL. Peak blood levels are achieved within approximately 2 hours for standard preparations of lithium, while peak levels for the sustained-release form are generally achieved within 4.5 hours (Jefferson et al., 1987). Baldessarini and Stephens (1970) demonstrated that complete absorption of lithium in adults usually occurs within 8 hours of its administration. Lithium circulates in the bloodstream unbound to protein and penetrates the blood-brain barrier within about one day of administration (Jefferson et al., 1987). It is excreted predominantly by the kidney, with approximately 80% being reabsorbed in the proximal renal tubules.

The proximal reabsorption of lithium competes with the proximal reabsorption of sodium. This becomes important when a patient is receiving a thiazide diuretic, which decreases the proximal reabsorption of sodium leading to increased lithium reabsorption and consequently increased lithium serum levels. In other words, the greater the sodium reabsorption in the proximal tubules, the less the lithium reabsorption and hence lithium serum level, and vice versa. In adults, the elimination half-life of lithium is approximately 24 hours, and over 60% of an acute dose is excreted within 12 hours. Children generally have a shorter elimination half-life of lithium (approximately 18 hours) because of their increased kidney-to-whole body ratio as compared to adults. In consequence, steady-state levels of lithium are reached sooner in children than in adults (Vitiello et al., 1988).

MECHANISMS OF ACTIONS

Although the exact mechanism of action of lithium remains unknown, recent investigations have considerably advanced our understanding of the method by

which lithium exerts its mood stabilizing effects. The effects of lithium on noradrenergic, dopaminergic, serotonergic, cholinergic, GABAergic (γ -aminobutyric acid), and glutaminergic pathways have lead investigators to hypothesize a second messenger, signal transduction mechanism of action. Lithium administration has been shown to alter the postreceptor coupling of signal-transducing G-proteins. Through G-proteins, many neurotransmitter receptors are linked to the enzyme phospholipase C, which hydrolyzes the membrane phospholipid phosphatidylinositol biphosphate (PIP₂) to produce two second messengers, diacylglycerol and inositol triphosphate (IP₃). DAG activates protein kinase C, and IP₃ releases Ca²⁺, which acts as a second messenger. PIP₂ is synthesized from free inositol. However, lithium blocks inositol monophosphatase, which inhibits neurons from generating free inositol (Lenox and Manji, 1995; Manji et al., 1999, 2000; Lenox and Hahn, 2000). Therefore, lithium inhibits second messenger pathways. Indeed, studies measuring platelet membrane phosphoinositides support this hypothesized mechanism of action (Soares et al., 2000b).

Recent advances in magnetic resonance imaging, in particular magnetic resonance spectroscopy (MRS), have made feasible the noninvasive measurement of brain neurochemicals. With MRS, molecules containing ¹H, ³¹P, ⁷Li can be quantified in vivo in human brain. Preliminary findings from ⁷Li MRS studies have assessed the pharmacokinetics of lithium in the brain and have in general found that brain lithium concentrations are correlated with serum levels and therapeutic response (Soares et al., 2000a; Kilts, 2000). To our knowledge, there have been no similar ⁷Li MRS studies of children and adolescents.

Proton MRS (¹H) has been used to study the neurobiological mechanisms by which lithium exerts its antimanic response in adults with bipolar disorder. The major chemicals measured in ¹H MRS spectra are *myo*-inositol (mI), choline (Cho), creatine (Cr), and *N*-acetyl-aspartate (NAA). ¹H MRS studies of *myo*-inositol in bipolar patients have been conflicting (Strakowski et al., 2000). Based on the hypothesized mechanism of action of lithium, a decrease in *myo*-inositol concentrations after lithium treatment is predicted. However, MRS studies of *myo*-inositol in patients with bipolar disorder have reported increases in the basal ganglia (Sharma et al., 1992) and no change in temporal brain regions (Silverstone et al., 1996) following lithium treatment. In contrast, Moore and colleagues (1999) studied the effects of lithium on prefrontal *myo*-inositol concentrations in depressed bipolar adults. Significant decreases of *myo*-inositol were observed in the right frontal lobe after 5–7 days of lithium treatment and were maintained after 3–4 weeks of initiating lithium. The reduction in *myo*-inositol was observed prior to the onset of clinical improvement.

Most recently, Davanzo and colleagues (2001) studied the effects of lithium in the anterior cingulate cortex of 11 manic children and adolescents with bipolar disorder. At baseline, bipolar children and adolescents had a higher *myo*-inositol/creatinine during the manic phase as compared to healthy volunteers. After a week of lithium treatment, patients exhibited a significant decrease in prefrontal

myo-inositol. Taken together, these data support a lithium-induced modification of the phosphoinositide cycle that may be specific to the prefrontal cortex.

Lithium has also been reported to alter gene expression, which may contribute to its potential neuroprotective effects. Recently, it has been shown that lithium increases expression of proteins that inhibit apoptosis. Additionally, lithium may alter interneuronal connectivity by inhibiting glycogen synthase kinase (GSK)-3 β , which reduces phosphorylation of *tau* protein and thereby enhances the binding of *tau* to microtubules and promotes microtubule assembly. Lithium also inhibits adenylyl cyclase and membrane transport of choline. Inhibition of adenylyl cyclase may contribute to abnormalities in thyroid-stimulating and anti-diuretic hormones, leading to lithium's side effects of hypothyroidism and nephrogenic diabetes insipidus (Manji et al., 1999).

A complete understanding of the clinical relevance of lithium's molecular mechanism of action remains unknown. Future studies examining the relationship between molecular biology and phenomenology will clarify the mechanisms by which lithium exerts its clinical effects.

INDICATIONS

Bipolar Disorder—Acute Mania

Lithium is the oldest and most well-studied mood stabilizer for adults with bipolar disorder. Five controlled studies of adults have demonstrated that lithium is superior to placebo in the treatment of acute mania (Bowden et al., 1994; McElroy and Keck, 2000). Additionally, data suggest that lithium is comparable and possibly superior to antipsychotics in the treatment of acute mania in adults and that lithium may exert antipsychotic effects in mania. There also have been more studies on the use of lithium in bipolar children and adolescents than any other mood stabilizer (Table 2). However, the majority of these studies were carried out with variable assessment protocols and in small samples without placebo control groups or in larger mixed samples (bipolar, ADHD, conduct) without adequate controls. The majority of these studies suggest a beneficial effect for lithium in many of these child and adolescent patients with bipolar disorder (see Table 3).

In a survey of the literature, Youngerman and Canino (1978) found that in open trials of lithium in children with bipolar disorder, the positive response rate was 66%, similar to that seen in adults treated with lithium. There have been six controlled trials of lithium in bipolar children and adolescents. Of these studies, four (Gram and Rafaelsen, 1972; Lena et al., 1978; McKnew et al., 1981; Delong and Nieman, 1983) used a crossover design. The average number of subjects in each of these studies was 18; response rates ranged from 33 to 80%. Dosages ranged from 600 to 1200 mg/day to achieve blood levels of 0.3–1.3 mEq/L. In general, lithium was well tolerated, with hand tremor as the only noted side effect.

TABLE 2 Studies of Lithium in Children and Adolescents with Bipolar Disorder

Study	<i>N</i>	Procedure	Response rate (%)
Annell, 1969	2	Case series	100
Dyson and Barcai, 1970	2	Case reports	50
Gram and Rafaelsen, 1971	18	Double-blind/cross	61
Feinstein and Wolpert, 1975	1	Case report	100
Dugas et al., 1975	9	Case series	89
Brumback and Weinberg, 1977	6	Case series	100
Horowitz, 1977	8	Case series	100
Lena et al., 1978	11	Double-blind/cross	54
Carlson and Strober, 1978	6	Case series	50
Davis, 1979	3	Case reports	100
Hassanyeh and Davison, 1980	7	Case reports	86
McKnew et al., 1981	6	Double-blind/cross	33
Rogeness et al., 1982	2	Case reports	50
Delong and Nieman, 1983	11	Double-blind/cross	80
Sylvester et al., 1984	2	Case reports	100
Delong and Aldershof, 1985	59	Case series	66
Hsu, 1986	8	Case reports	50
Hsu and Starzynski, 1986	14	Case series	78
Strober et al., 1988	50	Open trial	60
Varanka et al., 1988	10	Case series	100
Tomasson and Kuperman, 1990	1	Case report	100
Geller et al., 1998	25	Randomized, placebo-controlled	46.2
Biederman et al., 1998	31	Retrospective review	98
Kowatch et al., 2000	45	Randomized, open	42

In the only well-controlled, prospective study, which utilized current diagnostic criteria for bipolar disorder, Geller and colleagues (1998) administered lithium in a double-blinded, placebo-controlled fashion to 25 adolescents (12–18 years) with bipolar disorder and secondary substance dependency (most had alcohol and marijuana dependence). In this study, the adolescent's diagnosis of bipolar disorder preceded their substance abuse by several years. Adolescents were treated with a mean lithium dose of 1769 ± 401 mg/day. After 6 weeks of treatment, those subjects treated with lithium showed a significant decrease in their substance use and a significant improvement in their global assessment of functioning. The responders in the intent-to-treat sample had a mean serum lithium level of 0.88 ± 0.27 mEq/L compared with the nonresponder group at $0.79 \pm$

TABLE 3 Indications for Lithium in Child and Adolescent Psychiatry

FDA established:
Bipolar disorder—acute mania in patients > 12 years
Prophylaxis for bipolar disorder in patients > 12 years
Possible indications:
Bipolar disorder—acute mania in children < 12 years
Bipolar disorder—acute depression
Cyclothymia
Augmentation of tricyclic-refractory depression
Psychosis
Aggression and conduct disorder
ADHD
Substance abuse/dependence
OCD
Chronic hair pulling
Bulimia
Personality disorders

0.34 mEq/L. This report is the first well-controlled study that clearly demonstrated the efficacy of lithium carbonate in the treatment of bipolar adolescents with comorbid substance abuse.

However, Geller et al.'s study (1998) raised other unanswered questions concerning lithium's efficacy in pediatric bipolar disorder. Given the overall modest response rate, it is unknown whether an alternative mood stabilizer such as divalproex sodium may have shown greater efficacy.

In a more recent study, Kowatch and colleagues (2000) compared lithium to divalproex sodium and carbamazepine in the treatment of 42 acutely manic outpatients (6–18 years) during a 6-week random-assignment, open prospective investigation. Lithium was dosed at 30 mg/kg/day in three divided doses, and doses were titrated to a blood level of 0.8–1.2 mEq/L. The response rates for each mood stabilizer varied depending on the outcome measure. The mean response rates of the intent to treat sample were 40% and 53% for divalproex sodium, 46% and 38% for lithium, and 31% and 38% for carbamazepine as measured by a CGI change score of 1 or 2 and a greater than 50% change from baseline Young Mania Rating Scale, respectively. The response rate to lithium was similar to that found by Geller et al. (1998) (46%). Lithium was generally well tolerated, with only 3 of 14 (21%) subjects experiencing nausea, which was

the most common side effect for those treated with lithium. In the Geller et al. (1998) study, significant differences were found between the active and placebo groups for thirst, polyuria, nausea, vomiting, and dizziness. The most severe side effects were polyuria and polydipsia.

Veranka and colleagues (1988) treated 10 prepubertal children diagnosed with bipolar disorder with psychotic features with lithium carbonate doses up to 1800 mg per day (Jefferson et al., 1987). Significant improvement, including amelioration of mood and psychotic symptoms, occurred an average of 11 days after initiation of lithium. No antipsychotic medication was utilized. The lithium was well tolerated by these children. This is in contrast to usual clinical practice in bipolar adults with and without psychosis. Because lithium may take 7–10 days before exerting its effect, many advocate starting an antipsychotic agent concomitantly with the lithium to acutely control agitation. Although standard clinical practice in many settings, this treatment regimen has been called into question since lithium and some of the older antipsychotics, for example, haloperidol, can in combination increase the risk of extrapyramidal symptoms greater than either medication alone. This may be less of a concern with the increasing use of atypical antipsychotics, which have lower rates of extrapyramidal side effects.

Case History

A 16-year-old girl with no past psychiatric history but whose parents claimed that she “always ran a little higher than the rest of us” was admitted for inpatient psychiatric evaluation after running away from home and having a policeman apprehend her while she was directing traffic at 2 a.m. at a busy intersection without her clothes on. When she arrived in the emergency room, she alternately yelled at the emergency room staff that she had to get back to work downtown and would then spontaneously burst into singing the national anthem. She refused to let the emergency room staff examine her physically saying she was a special agent for the president and carried dangerous and priceless material that could not be “contaminated.” Her speech was pressured and she had racing thoughts. She reported that she had been unable to sleep for the past 7 days and had begun to work feverishly. She had completed all of her homework in every class for the remainder of the year. She had made several long distance phone calls after midnight to various acquaintances. She had also recently charged \$5,000 to her father’s credit card. Indeed, her father had found out about this the evening of admission and confronted his daughter. Although initially jovial during the encounter, she suddenly became upset and threw a knife at her father’s head and subsequently ran out the door. There was no history of drug or alcohol use, no prior depressive episodes, and no recent psychosocial stressor. Her parents en-

dorsed a family history of mood disorders. The patient's mother was taking Prozac for depression. An older sister had been diagnosed as having bipolar disorder and was being treated with lithium. She experienced a remarkable response on lithium therapy. A trial of lithium was initiated. Prior to its initiation, thyroid function tests, BUN/creatinine, U/A, electrolytes, CBC, urine pregnancy test, and urine drug screen were assayed and found to be normal. Lithium 300 mg tid was started. After 5 days on this dose, a plasma lithium level was drawn and found to be 0.6 mEq/L. She was still exhibiting prominent manic symptoms, therefore, her lithium dose was increased by 300 mg every 5 days to an ultimate dose of 1800 mg/day (lithium level 1.2 mEq/L). She tolerated this dose well without side effects.

Predictors of poor response to lithium include more than three prior mood episodes, a pattern of rapid cycling, "mixed mania" characterized by concurrent symptoms of mania and depression, and co-occurring attention-deficit hyperactivity disorder (ADHD) or personality disorder (Jefferson et al., 1987; Strober et al., 1998; McElroy and Keck, 2000; Swann et al., 2000). It has been reported that good responders to lithium therapy include those patients with onset of bipolar disorder in late adolescence and a positive family history of good response to lithium. Poor responders to lithium include younger prepubescent children with rapid cycling bipolar disorder. It should be noted, however, Strober and colleagues (1988) found that 15 adolescent-onset bipolar disorder patients who came from families with high rates of mood disorder responded poorly to lithium therapy. These adolescents had a history of behavior problems beginning in early childhood. Of those showing some response to lithium, it appeared much later, i.e., 6–8 weeks after the initiation of therapy, and was of lesser degree than the response reported in adolescents without prepubescent behavior problems. In a subsequent study Strober and colleagues (1998) found that adolescents with bipolar disorder and comorbid ADHD had a poorer response to lithium than adolescents without ADHD.

It is estimated that the prevalence of adolescent bipolar disorder is 1%. (Lewinsohn et al., 1995). However, there have been no epidemiological studies of prevalence rates of bipolar disorder in children. Studies of adults with bipolar disorder, report that the onset of symptoms commonly occurs during childhood (40%) (Lish et al., 1994). DSM-IV (APA 1995) does not have separate diagnostic criteria for children with bipolar disorder, despite the fact that the clinical manifestations of this disorder in children are often different than in adults. Bipolar children and adolescents commonly present in a mixed state, during which they exhibit mood lability, characterized by periods of silliness alternating with periods of intense depression and periods of irritability (Geller and Luby, 1997). In fact, Geller and colleagues (2000) found that 81% of bipolar children and adolescents had rapid cycling patterns characterized by brief manic periods last-

ing 4 or more hours. Although the presence of rapid cycling generally predicts poor response to lithium, children and adults with bipolar disorder have similar response rates to lithium (Geller et al., 1998; Kowatch et al., 2000). In the same sample of 93 bipolar children and adolescents, Geller and colleagues (2000) reported high rates of comorbid ADHD (81%) and other behavioral disorders (71%). Despite the high co-occurrence of juvenile mania and ADHD reported in this and other studies, the relationship between these disorders remains unclear (West et al., 1995; Biederman et al., 1996). Explanations for this high co-morbidity include juvenile mania with ADHD being a distinct form of early-onset bipolar disorder, ADHD being a prodrome of juvenile mania, or simply misclassification due to symptom overlap between the two conditions (Giedd, 2000). Comorbid ADHD occurs more commonly in prepubescent children as compared to pubescent children. Therefore, ADHD symptoms may be an age-specific manifestation of prepubertal-onset bipolar disorder (Geller et al., 2000). Nonetheless, because of the high rate of co-occurrence of these disorders and the perceived confusion in differentiating their clinical presentations, children with bipolar disorder are often initially treated with medications other than mood stabilizers (i.e., antidepressants and psychostimulants). In clinical practice, inquiries about the presence of mood disorders in a child's family, as well as the presence of mood syndromes and symptoms in the child, may help differentiate between ADHD with and without comorbid bipolar disorder. This difficult distinction is of paramount importance in establishing effective treatment strategies. Clearly, further longitudinal investigations are necessary to establish whether bipolar children become adults with bipolar disorder and to continue to examine the relationship between ADHD and bipolar disorder in children and adolescents.

Bipolar Disorder—Acute Depression

Lithium is currently considered the first-line therapy for the treatment of acute bipolar depression in adults, since recent evidence indicates that typical antidepressants may exacerbate the course of bipolar disorder by precipitating mixed or manic states (Compton and Nemeroff, 2000). However, in children and adolescents the efficacy of lithium in the treatment of bipolar depression is unknown. Recently, in a retrospective chart review Biederman and colleagues (2000) found that mood stabilizers were not effective in the treatment of bipolar depression. In a review of the literature on the treatment of nonpsychotic bipolar depression in adults, Zornberg and Pope (1993) reported that nine studies have compared treatment with lithium to placebo. Eight of these nine studies found lithium more effective than placebo, with a response rate of approximately 79%. For patients maintained on lithium therapy, the management of depressive symptoms should include evaluation of serum lithium and thyroid hormone levels. The level of lithium should be in the 1.0–1.2 mEq/L range. Patients may take up to 6–8 weeks

to respond. The clinician should always make sure to check thyroid function tests when a child or adolescent on lithium becomes depressed, since lithium can cause hypothyroidism, sometimes resulting in decreased energy levels and other depressive signs and symptoms. To our knowledge, there have been no studies examining the efficacy of lithium in the treatment of childhood and adolescent bipolar depression. Further prospective studies assessing the treatment of bipolar children and adolescents with an acute depressive episode are necessary.

Prophylaxis of Bipolar Disorder

As in adults, lithium is indicated for the prophylactic treatment of bipolar disorder in children and adolescents. Since the majority of patients with bipolar disorder experience recurrent episodes of illness, prophylaxis is advised. Studies in adults have shown that bipolar prophylaxis with lithium decreases the frequency and intensity of manic episodes in up to 80% of bipolar patients (Baastrup et al., 1970; Fieve et al., 1976; Prien et al., 1984). In the only lithium prophylaxis study in adolescents, Strober and colleagues (1990) conducted an 18-month naturalistic follow-up study of 37 adolescents whose bipolar disorder had been stabilized with lithium during hospitalization. They reported that despite intensive follow-up, 35% of these patients discontinued lithium, and 92% of those who discontinued subsequently relapsed, supporting the possible prophylactic effect of lithium. The mean lithium serum level in the 24 (65%) patients who continued their maintenance lithium therapy during the entire 18-month follow-up period was 0.79 mEq/L (range = 0.6–1.2 mEq/L). Reasons for discontinuation of lithium were not described (Strober et al., 1990). Generally, if a child or adolescent has responded well to lithium, it is advisable to keep him or her on a maintenance dose of lithium for a minimum of 12–18 months and then if the patient is euthymic or asymptomatic to gradually taper lithium over a 2- to 3-month period (Kowatch and Bucci, 1998). Careful monitoring for efficacy versus toxicity is good clinical practice. Compliance may be a major issue in adolescence, and communication with the patient and family about the medication and its side effects is crucial.

Cyclothymia

Cyclothymia is characterized by periods of hypomania alternating with periods of depression not severe enough to meet criteria for a major depressive or manic episode. In children and adolescents only a one-year period of alternating moods, i.e., depression and hypomania, is required, as opposed to the two-year period required for the diagnosis in adults (APA, 1995). In patients diagnosed with cyclothymia, there is often a positive family history for mood disorders (Howland and Thase, 1993). There are no treatment data in children and adolescents with cyclothymia. In general, studies of adults with cyclothymia provide some evi-

dence to support the efficacy of lithium in treating cyclothymia, although the response may be less than that of other bipolar disorders (Howland and Thase, 1993). Of interest, Peselow et al. (1982) divided cyclothymic patients into groups having a positive and negative family history of mood disorders and found a trend for a better lithium response in those with a family history of mood disorders. Therefore, investigation into family history might be helpful. Clinically, a lithium trial is reasonable for children and adolescents with cyclothymia, although controlled studies are necessary.

Unipolar Depression

Numerous controlled studies of adults have shown that lithium is effective in treating acute episodes of unipolar depression as well as reducing relapses when given as maintenance therapy (Neubauer and Bermingham, 1976; DeMontigny et al., 1981, 1983; Heninger et al., 1983; Louie and Meltzer, 1984; Prien et al., 1984; Schrader and Levien, 1985; Garbutt et al., 1986; Pope et al., 1988; Ryan et al., 1988; Strober et al., 1992). Long-term studies in adults have shown that lithium may also reduce suicide rates (Coppen, 2000; Tondo and Baldessarini, 2000). However, lithium is generally not as effective as antidepressants for the treatment of unipolar depression. Geller and colleagues (1994) evaluated the efficacy of lithium vs. placebo in the treatment of adolescents with major depression refractory to tricyclics and who had a family history of bipolarity. The rationale for this study was that prepubescent children with major depressive disorder and a family history of bipolar disorder commonly develop bipolar disorder. However, they found no difference in response between groups, suggesting that lithium may not be effective in the treatment of patients with prepubescent depression and who are at high risk for developing bipolar disorder.

Lithium's role as an augmenting agent for refractory unipolar depression has been well established in adults. However, there have been only two studies examining the treatment of depressed children and adolescents with a combination of lithium and a tricyclic antidepressant. In the first study, Ryan and colleagues (1988) conducted a retrospective chart review of 14 adolescents (14–19 years), diagnosed with unipolar depression who were subsequently treated with a tricyclic antidepressant (desipramine, nortriptyline, amitriptyline)/lithium combination after an inadequate response to a tricyclic antidepressant alone. Lithium dosages ranged from 600 to 1200 mg/day and mean lithium serum level was 0.65 mEq/L. Six of the 14 patients (over 40%) had a good response to lithium augmentation of a tricyclic. Moreover, all of the adolescents tolerated the combination well and without toxicity. Obviously, conclusions from this report are limited, since it was an open trial with only 14 patients. Nonetheless, with the poor results obtained from tricyclic antidepressant treatment in children and adolescents, these results are intriguing and suggest that there may be a population

of adolescents who respond to the tricyclic/lithium combination. Ryan and colleagues observed that the duration of treatment with the tricyclic antidepressant before the lithium was added was 6–8 weeks, which was longer than the average of 3 weeks in the adult studies. In fact, 7 adolescents continued to show improvement in their symptoms as long as 6 weeks after the lithium augmentation. This was not a placebo-controlled crossover trial, so the possibility that the patients improved with time from the antidepressant as opposed to from the addition of lithium cannot be discounted (Ryan et al., 1988).

In the second study, Strober and colleagues (1992) demonstrated that 2 of 24 adolescents who were partial imipramine responders showed amelioration of symptoms within the first week of starting lithium, and 8 other patients showed partial improvement during the 3-week trial, as compared to only 1 of 10 controls who continued to receive imipramine monotherapy. Mean lithium serum level upon completion of the study was 0.89 mEq/L. The two most frequent side effects were polyuria and tremor. This study suggests that lithium may be well tolerated and effective as an augmenting agent for the treatment of adolescents with major depression.

Using the combination of fluoxetine and lithium in the treatment of acute depression is generally safe and effective for adults (Pope et al., 1988; Bauer et al., 1996). There are currently no studies involving lithium augmentation of SSRIs in the treatment of childhood and adolescent major depression. However, this combination might prove to be an effective treatment strategy for children with refractory major depression.

In contrast to bipolar depression prophylaxis where lithium is considered to be the drug of choice, most psychiatrists do not use lithium as a first-line agent for prophylaxis of unipolar depression in adults. Prien and colleagues (1984) in a large multicenter study observed that lithium was effective in prophylaxis for unipolar depression only when the most recent depressive episode had been mild and that lithium was not significantly better than placebo in prophylaxis against unipolar depression when the prior episode had been severe. There are no data on lithium's use in the prophylaxis of major depression in children and adolescents. Lithium's role as an adjunct to antidepressant therapy, as monotherapy for acute depressive episodes, and perhaps ultimately in prophylaxis against recurrent depression with an antidepressant deserves further evaluation.

Psychosis

As previously discussed, Veranka and colleagues (1988) used lithium to successfully treat 10 prepubertal children 6–12 years of age with manic episodes, family psychiatric histories, and psychotic symptoms. All of the children improved when treated with lithium alone (mean dose = 1270 mg/day, 40 mg/kg/day). Manic

and psychotic symptoms improved an average of 11 days after lithium was started. In the past, since lithium often takes 7–10 days to take effect, antipsychotics such as haloperidol were often given concomitantly, short term until the lithium began to exert its effect. However, because of the potential for extrapyramidal side effects and tardive dyskinesia, using this combination was less desirable in children. More recently, with the development of atypical antipsychotics, which appear to have less severe side effects, this is less of an issue. Additionally, since atypical antipsychotic medications have mood-stabilizing properties (McElroy and Keck, 2000), treatment with a mood stabilizer and an atypical antipsychotic may be optimal for the initial treatment of psychosis associated with mood disorders. However, controlled data in children and adolescents are lacking.

Schizoaffective disorder is seen in patients who have discrete periods of psychosis without affective symptoms, but who have prominent mood syndromes (APA, 1995). In adults, lithium is often used as an adjunct to a neuroleptic (McElroy et al., 1999). There have been eight studies comparing lithium with standard antipsychotic agents. (McElroy et al., 1995). In general, typical antipsychotics and lithium had comparable efficacy, except in agitated patients, for which antipsychotics were superior to lithium. Moreover, the addition of lithium to a typical antipsychotic is superior to the addition of placebo, suggesting that combination treatment may be most effective (McElroy et al., 1995). However, with the development of atypical antipsychotics, which have both mood-stabilizing and antipsychotic properties, monotherapy may be the treatment of choice. There are no treatment data in children and adolescents, and there have been virtually no investigations on the validity of this diagnosis in childhood and adolescence.

Schizophrenic patients often suffer from mood symptoms. Psychosis of sudden onset, especially if the family history is positive for mood disorder, may warrant a trial of lithium (Arana and Rosenbaum, 2000). It has been reported that nearly all children and adolescents with major depression with psychotic features go on to develop bipolar disorder. This does not necessarily mean that lithium is the first drug of choice when a patient presents depressed and psychotic but that careful monitoring for mania is warranted. This is especially true if an antidepressant is started. Antidepressants may precipitate mania, particularly in a biologically vulnerable patient (see Chapters 8–11).

In summary, when mood symptoms are present during a psychotic process, lithium therapy should be considered. In fact, lithium's mood-stabilizing properties may be particularly beneficial in psychotic patients prone to shifts in their mood. Lithium is frequently added to schizophrenic adult patient regimens, although there are few data to support its efficacy in the absence of mood symptoms (Soares and Gershon, 2000). Children and adolescents with psychotic symptoms may benefit from the addition of lithium to an antipsychotic. However, there are no controlled studies supporting this practice.

Aggressive Behavior and Conduct Disorder

Lithium has been studied extensively in the treatment of aggression associated with a wide variety of childhood disorders, including pervasive developmental disorders, disruptive behavioral disorder, and mental retardation (Greenhill et al., 1973; Schiff et al., 1982; Bennett et al., 1983; Campbell et al., 1984a, b; Platt et al., 1984; Vetro et al., 1985; Carlson et al., 1992; Malone et al., 1994, 1995, 1998; Rifkin et al., 1997; Weller et al., 1999). Schiff and colleagues (1982) demonstrated that lithium was effective in decreasing episodic and explosive behavior in patients with antisocial personality disorder, particularly in those with a family history positive for mood disorders. Greenhill and colleagues (1973) used lithium to treat nine children (6–16 years) with hyperactivity, aggression, and “giddy” behavior and noted clinical improvement in only two of these children (mean dosage = 1133 mg/day). These two children’s behavior deteriorated when the lithium was removed. The other children, however, got worse or showed no improvement. The authors noted that the two children who responded had more mood “lability, euphoria, and depression” symptoms than those children who did not respond to lithium therapy, indicating that perhaps they had an underlying mood disorder accounting to their response to lithium.

DeLong and Aldershof (1987) used lithium to treat children with behavioral disorders who had a variety of concomitant neurological disorders including mental retardation and noted a significant decrease in aggression, explosive outbursts, and encopresis. The decrease in encopresis was not an anticipated finding. Encopresis, is, however, often associated with disruptive behavior disorders, and perhaps the amelioration of the behavioral symptoms resulted in the secondary decrease in encopresis.

Vetro and colleagues (1985) used lithium to treat 17 very aggressive and actively destructive children 3–12 years of age who had severe social maladjustment difficulties. Ten of the 17 children were refractory to haloperidol combined with behavioral, individual, and family therapy. At mean serum lithium levels of 0.68 mEq/L, Vetro and colleagues observed 13 of the 17 children exhibited decreased aggressiveness and better social adjustment to the environment. The children needed continuous treatment with lithium for time periods of greater than 6 months for maximal efficacy. The authors also pointed out that three of the four cases that did not demonstrate clinical improvement had been noncompliant with the medication regimen. Although these studies suggest that lithium is effective in treating aggression, these studies are limited in that they did not use DSM diagnoses to categorize patients.

Several double-blind, placebo-controlled studies suggest that lithium is effective in treating aggression associated with conduct disorder (Campbell et al., 1984a, b). Lithium was noted to be equally efficacious and cause fewer and less

toxic side effects than haloperidol in one study that compared lithium, haloperidol, and placebo. However, lithium treatment was associated with decreased performance on the Porteus Maze test but did not impair short-term memory and performance on other cognitive tests (Platt et al., 1984). In contrast, Rifkin and colleagues (1997) conducted a 2-week trial in adolescents with conduct disorder and found neither lithium nor placebo effective in treating aggression. Possible explanations for the differences in results among studies include the age of the subjects and the length of treatment, which was younger and longer, respectively, in the earlier studies. Additionally, different rating scales were used to measure aggression.

In a more recent study, Malone and colleagues (1994) evaluated the efficacy of lithium in an open-label study of 8 children and adolescents (9–17 years) with conduct disorder using the Overt Aggression Scale and the Global Clinical Consensus Rating, a more general measure of behavior change. They found that both the Overt Aggression Scale and the Global Clinical Consensus Rating demonstrated that lithium (mean dose = 1350 ± 227 mg/day, mean serum level = 1.05 ± 0.17 mEq/L) was effective in decreasing aggression.

Further controlled trials of lithium in the treatment of well-characterized diagnostically homogeneous populations of children and adolescents with disruptive behavioral disorders are necessary.

ADHD

Lithium is a last-line treatment option in children and adolescents with ADHD. Stimulants are the pharmacological treatment of choice (see Stimulant section) followed by the antidepressants, i.e., desipramine (Antidepressant section) and clonidine (see Clonidine section). It is only when these more standard and more efficacious treatments of ADHD are unsuccessful that alternative medications such as lithium, carbamazepine, and antipsychotics such as haloperidol might be considered. Some advocate a lithium trial for children and adolescents with refractory ADHD who have a family history of mood disorder or who are exhibiting mood type symptoms along with their ADHD. However, investigation to date has shown that lithium is ineffective when used to treat children diagnosed with ADHD (Strober et al., 1998; Greenhill et al., 1973). Since the differential diagnosis between ADHD and bipolar disorder, especially the rapid-cycling type, may be difficult and the two disorders commonly coexist, further study of lithium in the treatment of ADHD with and without bipolar disorder is warranted.

Substance Abuse

See Chapter 19.

Obsessive-Compulsive Disorder

Lithium may potentiate antidepressant-induced increase in serotonin. Therefore, lithium has been used as an augmenting agent for the treatment of obsessive-compulsive disorder (OCD). There have been numerous case reports of lithium's effectiveness in the augmentation of imipramine, clomipramine, desipramine, and doxepin in patients with OCD. In one study, the addition of open-label lithium to ongoing fluoxetine treatment led to 75% of patients showing improvement (McDougle, 1997). In contrast, double-blind, placebo-controlled studies of lithium augmentation show no significant long-term improvement in OCD symptoms. Therefore, based on controlled data, treatment of SSRI-refractory OCD with lithium does not appear to demonstrate response rates similar to lithium augmentation in the treatment of depression (McDougle, 1997).

Chronic Hair Pulling

Christenson and colleagues (1991) evaluated open-label lithium in the treatment of adults with "hair pulling" and reported that 8 of 10 patients exhibited improvement as measured by hair regrowth. Therefore, lithium may be an effective treatment for tricotillomania. Further controlled studies in children are needed.

Bulimia

Hsu (1984) conducted a study in which 14 bulimic patients were treated with lithium. While 12 of the 14 patients showed moderate to marked improvement on lithium, 10 had a coexistent mood disorder. Co-occurring mood disorders are not, however, uncommon in patients with eating disorders. Patients with eating disorders often abuse laxatives and diuretics, which can result in lithium toxicity in patients receiving lithium. Therefore, treatment with lithium in patients with eating disorders should be approached with caution.

Personality Disorders

The use of lithium in personality disorder patients is controversial. This is complicated by the fact that coexistent mood disorders are not uncommon in patients with personality disorders so that it is often difficult to delineate specific medication effects on the personality disorder. In general, personality disorders are not indications for lithium's use. If there is a coexistent mood disorder, e.g., bipolar disorder, then the mood disorder should be treated. Obviously, an axis I mood disorder can negatively impact on an axis II personality disorder, and vice versa, so that ameliorating symptoms of the mood disorder may result in improvement in some personality symptoms.

Comorbidity with personality and mood disorders is associated with decreased responsiveness to lithium in adolescents and increases the likelihood of

postdischarge neuroleptic treatment (Kutcher et al., 1990). Many practicing clinicians are reluctant to diagnose adolescents with personality disorders. As with adults, it is probably best to treat mood disturbances as indicated but not to directly target personality/character pathology with lithium.

CONTRAINDICATIONS

For contraindications, see Table 4.

Pregnancy

Lithium use, particularly in the first trimester of pregnancy, significantly increases the risk of cardiac deformities and malformations. Ebstein's anomaly, the downward displacement of the tricuspid valve, is the most well-known and most common anomaly associated with lithium use during the first trimester (Cohen et al., 1994). A recent review found this risk to be much lower than previously reported, but still several times greater than the general population (Cohen et al., 1994). Thus, it is crucial to emphasize to adolescents and family members the importance of using contraception while taking lithium. It is also crucial to emphasize the importance of informing the treating physician if the patient intends to become pregnant or accidentally becomes pregnant while taking lithium. Because of the high risk for side effects associated with lithium, consultation with a treating physician is essential.

Renal Disease

Lithium is relatively contraindicated in children and adolescents with renal disease as it is primarily excreted by the kidneys.

TABLE 4 Contraindications to Lithium
Use in Children and Adolescents
Psychiatry

Absolute:

Allergic drug reaction (rare)

Relative:

Pregnancy

Renal disease

Cardiovascular disease

Thyroid disease

Severe dehydration/sodium depletion

Cardiovascular Disease

Lithium is relatively contraindicated in children and adolescents with cardiovascular disease as lithium has been associated with AV block and other cardiovascular side effects. Its use in such patients can significantly raise the likelihood of lithium toxicity developing (Jefferson and Greist, 1991).

Thyroid Disease

Thyroid disease is no longer felt to be a contraindication to lithium's use. Carefully monitoring thyroid function and using supplemental thyroxine (synthroid) when necessary is recommended.

Severe Dehydration/Sodium Depletion

Severe dehydration and/or sodium depletion are relative contraindications to lithium's use in children and adolescents due to the very high risk of lithium toxicity.

History of Hypersensitivity/Allergy

A child or adolescent who experienced an allergic reaction to lithium should not receive lithium in the future. However, such reactions are uncommon with lithium.

Patients on Thiazide Diuretics

Lithium is not contraindicated in patients taking thiazides. However, alternative dosing strategy is necessary in these patients (see below).

Electroconvulsive Therapy

Concurrent administration of lithium with ECT may prolong the muscular blockade of succinylcholine (Fink, 1988). Therefore, prior to initiating ECT, lithium should be discontinued.

SIDE EFFECTS

In general, at therapeutic doses lithium is well tolerated in children and adolescents. Side effects occur more commonly in younger children than older children, especially in those with neurological and medical illnesses (Campbell, 1991). Most commonly, side effects occur during the initial week of lithium therapy and are associated with high mg/kg doses and high lithium levels (Hagino et al., 1995) (Table 5).

TABLE 5 Side Effects of Lithium

Common:
GI (nausea/vomiting, diarrhea)
Tremor
Leukocytosis
Malaise
Uncommon:
Renal (polydipsia/polyuria)
Ocular irritation/stomatitis
Hypothyroidism/nontoxic goiter
Dermatological
Cardiovascular
Weight gain/edema
NMS/encephalopathic syndrome
Diabetes
Hair loss
Growth and development

Gastrointestinal

General GI distress is a frequently encountered early side effect of lithium therapy (Jefferson and Greist, 1991). Signs and symptoms include nausea, vomiting, diarrhea, abdominal discomfort, and feelings of malaise. These effects are usually short-lived and may be related to rapidly increasing plasma lithium levels. Having the patient take lithium with meals may help ameliorate GI discomfort. Starting with a low dose and increasing the dose gradually may also be helpful. Certain slow-release lithium preparations (e.g., Lithobid) are better tolerated. However, slow-release lithium preparations may be more likely to cause diarrhea. Cessation of lithium therapy should be considered if its use results in significant electrolyte and volume depletion via emesis and/or diarrhea. GI discomfort that emerges late in the treatment with lithium may be a sign of toxicity, and a lithium level should be checked.

Neurological

A fine tremor is often seen early during lithium treatment and usually signifies that lithium is at therapeutic levels in the bloodstream (Jefferson and Greist, 1991). This is in contrast to the gross tremor seen with lithium toxicity.

Benign intracranial hypertension (Arana and Rosenbaum, 2000) has been reported in some adult patients treated with lithium. Although rare, patients complain of headaches, papilledema, and blurred vision. Fundoscopic examination should be considered in patients complaining of these symptoms.

Although lithium produces electroencephalographic changes, in general it does not appear to reduce seizure threshold (Arana and Rosenbaum, 2000). Other central nervous system side effects include, headache, ataxia, and dysarthria.

Renal Dysfunction

Polyuria, polydipsia, and enuresis may occur at any time during lithium therapy due to its direct effect on the kidneys. Polyuria may occur in up to 50–70% of patients taking lithium. Sometimes this can result in a nephrogenic diabetes insipidus (NDI)-like syndrome. This side effect may necessitate decreasing the dose, discontinuing the lithium, or, more rarely, treating the NDI with hydrochlorothiazide or amiloride. If hydrochlorothiazide is necessary, the lithium dose must be decreased to avoid lithium toxicity (see below). Patients who suffer from severe polyuria secondary to lithium have been reported to excrete several liters of urine per day. Therefore, it is essential that kidney function be monitored, since lithium can occasionally result in a decreased glomerular filtration rate due to glomerular sclerosis and tubular atrophy (Vestergaard, 1980).

Ocular Irritation/Contact Stomatitis

Ocular irritation and/or contact stomatitis may result when lithium is secreted into body fluids (Lapierre and Raval, 1989).

Hypothyroidism/Nontoxic Goiter

Lithium interferes with thyroid hormone production by inhibiting iodine uptake, tyrosine iodination, and release of T3 and T4. Inhibition of adenylyl cyclase in thyroid cells may also occur. Lithium can produce hormonal side effects, including hypothyroidism and a nontoxic goiter (Herskowitz, 1987). Decreased circulating thyroid hormones, T3 and T4, and elevated thyroid stimulating hormone (TSH) may result. Vetro and colleagues (1985) observed that two of the children in their sample developed nontoxic goiter after being on lithium for 1.5–2 years. Hyperthyroidism has been reported with lithium use in adults but occurs far less frequently than does hypothyroidism. Thyroid monitoring should occur every 6 months or more frequently as warranted. Should hypothyroidism develop, it may be treated with hormone replacement and treatment with lithium should continue.

Dermatological

Dermatological side effects can be particularly problematic for adolescent patients. The most common dermatological side effects are an increase in acne vulgaris and maculopapular eruptions. Less commonly, exacerbation and/or aggravation of psoriasis may occur. Males may be more vulnerable to dermatological side effects than females (Chan et al., 2000).

Hair loss is a rare side effect of lithium treatment but has been reported in childhood (Wagner and Teicher, 1991). When this occurs, it is important to check thyroid hormone levels as hypothyroidism is also associated with hair loss.

Weight Gain and Edema

Weight gain and edema are common side effects associated with lithium's use. Weight gain may be particularly troublesome for adolescents. Lithium is thought to result in weight gain through its insulin-like effects on carbohydrate metabolism. Further investigation of weight gain associated with lithium and other psychotropic medications in children and adolescents is warranted (Jefferson and Greist, 1991).

Leukocytosis

Lithium causes a clinically insignificant increase in white blood cell count between 10,000 and 15,000 cells/mm³ with an increased polymorphonuclear leukocytes. There is no impairment in function of leukocytes (Reisberg and Gershon, 1979).

Cardiac

Lithium is associated with EKG changes, such as T-wave inversion or flattening. Generally, these changes are benign and are reversible following lithium discontinuation. Lithium may also result in arrhythmias, typically in patients with preexisting cardiac disease. If arrhythmias are discovered, electrolytes and thyroid hormones should be evaluated (Arana and Rosenbaum, 2000).

Malaise and Fatigue

Malaise and fatigue are common complaints of patients receiving lithium. This does not always imply toxicity (see overdose and toxicity section). Children and adolescents may complain of feeling sluggish, tired, and uncomfortable. Sometimes this decreases with time as the child adjusts to the medication. In other cases, adjusting the dose is helpful. Beginning treatment with a low dose and increasing gradually may also help decrease some of these side effects.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) has been seen in patients treated with a combination of lithium and antipsychotic medications (PDR, 2001). In a few patients treated with lithium and a neuroleptic, a full-blown encephalopathic syndrome has developed, which is characterized by weakness, lethargy, fever, confusion, extrapyramidal side effects, increased white blood cell count, BUN, serum

enzymes, and fasting blood sugar. It is essential to monitor patients receiving both lithium and neuroleptics extremely closely for the presence of neurotoxicity, since this syndrome can result in death. This usually occurs at toxic plasma lithium levels. Therefore, careful monitoring of lithium plasma blood levels is essential when haloperidol and lithium are co-administered. If such symptoms occur, lowering the dose of lithium or discontinuing the medication may be necessary.

Diabetes

Lithium may occasionally accelerate the development of diabetes (Herskowitz, 1987).

Growth and Development (Calcium)

It is known that lithium increases serum calcium and parathyroid levels by interfering with calcium metabolism and mobilizing calcium from immature bones. Moreover, lithium decreases the sensitivity of cultured parathyroid cells to calcium, so that more hormone is secreted for the same level of calcium. It is, therefore, recommended that children who are treated with lithium undergo regular physical examinations specifically evaluating growth and development. Moreover, some investigators believe that calcium, phosphorus, and alkaline phosphatase need to be monitored in children who are still growing (Mak et al., 1998).

Overdose/Toxicity

Lithium toxicity is very closely related to serum lithium levels and can occur at doses close to therapeutic levels (PDR, 2001). Moreover, lithium has a low therapeutic index and can be lethal following an overdose. Therefore, it is imperative that lithium only be prescribed to families that are compliant with medication regimens. It is important to remember that although lithium overdose may result in lithium toxicity, the most common cause of toxicity in compliant patients is a change in sodium balance leading to sodium depletion (Arana and Rosenbaum, 2000). Sodium depletion elevates lithium levels. In fact, the clinician must monitor the patient closely to determine any condition that can alter the sodium balance such as dehydration and change in diet. The patient and family should be informed that it is important for the child or adolescent on lithium to get sufficient amounts of table salt and liquids. Particularly in hot weather, it is important that children and adolescents stay well hydrated. Although mild exercise may be associated with lithium level elevation, strenuous exercise appears to be associated with a decrease in lithium level. Jefferson and colleagues assessed four athletes in good health and who were placed on stable doses of lithium for a period of one month before they competed in a 20-km race. After the race, the four patients were found to be dehydrated, but instead of having increased serum lithium lev-

els, their serum lithium levels decreased by 20%. Interestingly, the sweat-to-serum ratio for the lithium cation was four times greater than that for the sodium ion (Jefferson et al., 1987). It was concluded that strenuous exercise that results in large amounts of perspiration is more likely to necessitate an increase or no change in the lithium dose, since serum lithium levels after this type of exercise appeared to decrease rather than increase. Nonetheless, Jefferson and associates still recommend careful monitoring of the fluid/electrolyte status of patients on lithium who engage in strenuous exercise.

There are different degrees of lithium toxicity: mild, moderate, and severe (Arana and Rosenbaum, 2000). Mild intoxication is typically manifested by subtle symptoms such as GI distress and dizziness. In these cases, lithium should be held until the level returns to the therapeutic range (Arana and Rosenbaum, 2000). It is important to search for the cause of the increased level, i.e., noncompliance, overdose (accidental or purposeful), or concomitant medications. If no obvious cause for the increased level and toxicity is found, a renal workup is indicated, which should include a urinalysis, electrolytes, BUN/creatinine, creatinine clearance, urinary sodium, and 24-hour protein. With moderated or severe lithium toxicity, the patient needs to be admitted to the hospital so that sodium can be administered while frequent lithium levels are monitored (Arana and Rosenbaum, 2000).

Acute Lithium Intoxication

Lithium levels above 3 mmol/L can be life-threatening and represent a medical emergency (Arana and Rosenbaum, 2000). It is important to emphasize that the reversibility of lithium intoxication is directly related to the serum level of lithium and the length of time it remains elevated. Thus, it is critical that measures to reduce the toxic level be initiated immediately. It is also important to note that even with very high lithium serum levels and after a significant overdose, symptoms may be quite mild and subtle. The physician must not be lulled into a false sense of security. Severe symptoms can come on rapidly and, without warning, result in the death of the patient. Therefore, it is important to counsel patients and their families about the importance of looking for any early warning signs of lithium toxicity and the need to tell the physician immediately if they occur. Signs and symptoms of serious lithium intoxication include ataxia, dysarthria, gross tremor, delirium, hallucinations, seizure, coma, renal failure, diarrhea, and neuromuscular flaccidity (Arana and Rosenbaum, 2000). Patients who survive severe lithium toxicity may suffer permanent impairment in memory, gait, and other functions (Schou, 1984).

There is no specific antidote to lithium overdose (Arana and Rosenbaum, 2000). However, it is believed that in cases of lithium poisoning, treatment should attempt to remove the excess lithium from the body. As with any intended or

accidental overdose, the clinician should obtain a toxicology screen to see if the patient has taken other drugs. Gastric lavage should occur in acute overdose patients. Lithium levels are often quite high in gastric secretions, so gastric aspiration is very important (Arana and Rosenbaum, 2000). It is also essential that correction of the fluid and electrolyte imbalance be promptly initiated. When lithium levels are less than 3 mmol/L and the signs of intoxication are mild, fluid and electrolyte imbalance can be corrected by administering IV normal saline at rates of 150–200 mL/hour as long as the patient produces adequate urine (Arana and Rosenbaum, 2000). At lithium levels greater than 3 mmol/L and with evidence of severe toxicity, i.e., if there is minimal urine output and/or renal failure, dialysis is necessary. Hemodialysis is the preferred treatment as it rapidly removes lithium ions from the toxic patient. Urea, mannitol, and aminophylline are capable of significantly increasing the excretion of lithium (PDR, 2001). It is very important to monitor frequent lithium levels during dialysis, as lithium will reequilibrate from the tissues after hemodialysis treatment (Arana and Rosenbaum, 2000). Targeted lithium levels are ≤ 1 mmol/L, 6 hours after dialysis. When such levels are obtained, the dialysis can be stopped. As in all life-threatening situations, it is also important to monitor the patient's airway, breathing, and circulation.

ABUSE

There appears to be virtually no risk for recreational abuse of lithium.

DRUG INTERACTIONS

It is essential to inform patients that over-the-counter nonsteroidal anti-inflammatory drugs, such as ibuprofen, potentially increase lithium levels, and if possible acetaminophen should be taken instead. Additionally, parents should be informed that commonly prescribed antibiotics such as ampicillin and tetracycline as well as thiazide diuretics may also increase serum lithium levels. Metronidazole may cause renal toxicity when used in combination with lithium (Arana and Rosenbaum, 2000). (For drug interactions, see Table 6.)

AVAILABLE PREPARATIONS

Several slow-release preparations of lithium are available (Table 7). In the United States, these include Lithobid and Eskalith CR. Some studies comparing slow-release products with conventional forms have demonstrated differences in bioavailability, site and rate of absorption, and rates of side effects. Slow-release formulations tend to have lower rates of tremor and nausea but may have higher rates of diarrhea if taken on an empty stomach because of incomplete absorption and the presence of lithium ion in the distal intestine (Lyskowski and Nasrallah,

TABLE 6 Lithium Drug Interactions

Increase serum lithium levels:
Antibiotics
Carbamazepine
Diuretics
SSRIs
Nonsteroidal anti-inflammatory agents
Decrease serum lithium levels:
Acetazolamide
Caffeine
Osmotic diuretics
Theophylline
Interact with lithium to produce sedation and/or confusional states:
Alcohol
Antihypertensives
Antipsychotics (especially haloperidol)

1981). However, other studies indicate that rates of side effects may not differ in patients taking regular and slow-release formulations (Lyskowski and Nasrallah, 1981).

INITIATING AND MAINTAINING TREATMENT

Before treatment with lithium is initiated in children and adolescents, a premedication workup is required. This workup is similar to that performed on adults. Children and adolescents must have a complete history and physical examination performed by their primary medical physician. Weight should be monitored at

TABLE 7 Available Preparations of Lithium

Generic	Proprietary	Strength
Lithium carbonate	Eskalith	300 mg
Lithium carbonate	Lithium carbonate	300 mg
Lithium carbonate	Lithonate	300 mg
Lithium carbonate	Lithotabs	300 mg
Lithium carbonate, slow-release	Eskalith CR	450 mg
Lithium carbonate, slow-release	Lithobid	300 mg
Lithium citrate syrup	Cibalith	8 mEq/5 mL (equal to one 300 mg tablet)

every visit, and children with significant weight gain should be considered for alternative medications or the addition of other medications that may help to decrease the weight gain. Laboratory assessment should include performing a pregnancy test on every female patient. Counseling about the use of birth control is necessary. Additionally, it is important to evaluate all patients for evidence of kidney and thyroid disease before lithium is started. In healthy patients this merely requires checking a urinalysis, BUN, creatinine, thyroid-stimulating hormone (TSH), and free T4 (Tueth and Evans, 1998). If renal anomaly is noted prior to initiating lithium therapy, it is probably best to avoid lithium and try an alternative medication such as divalproex sodium. If all other alternatives have been exhausted and the clinician believes that lithium is essential to the patient's functioning, e.g., a very strong positive family history of response to lithium or the patient has responded well to lithium in the past, then consultation with a nephrologist is recommended. If it is decided to initiate lithium therapy, very careful monitoring of kidney function is required.

Once a stable dose of lithium is achieved, checking kidney function one week later is recommended. If this is normal, assessing kidney function every 6 months is sufficient. If an abnormality occurs, consultation with a medical specialist and obtaining laboratory tests, including a urinalysis, with particular attention to specific gravity, BUN and creatinine, creatinine clearance, 24-hour urine protein, and urinary sodium is recommended. While the patient is on lithium, the patient and family should be active participants in monitoring renal function, and if any abnormality is noted, such as increased frequency of urination, drinking more fluids than usual, or complaining of increased thirst, the parents should be instructed to call the psychiatrist immediately and hold the lithium until they speak with the doctor and/or have their child assessed.

Jefferson and Ackerman (1987) found that as many as 15% of patients receiving lithium therapy will show increased TSH levels. Lithium causes these thyroid anomalies by reducing thyroid hormone release leading to decreased levels of T3, T4, and protein-bound thyroid hormone and increased TSH and I131 levels. Therefore, it is essential to determine baseline thyroid function prior to initiating lithium therapy by checking T4, T3, T3RU, and TSH levels. Some investigators recommend checking antithyroid antibodies since hypothyroidism secondary to lithium may be related to a preexisting Hashimoto's thyroiditis (Spratt et al., 1982). Abnormalities do not necessarily preclude treatment with lithium. Elevated TSH levels are felt to be the most sensitive index for hypothyroidism. If this occurs it is best to repeat the level and consult an endocrinologist. If the level remains elevated, the clinician can either use another medication and/or, upon consultation with the endocrinologist, consider treating the hypothyroidism with thyroxine (synthroid) while the lithium is administered. Frequent monitoring of lithium blood levels and thyroid function is necessary. The patient

should also be monitored for signs of hypothyroidism, i.e., thinning hair, dry skin, heat/cold intolerance, and decreased energy.

It should be noted, however, that transiently abnormal thyroid function tests without coexistent thyroid pathology have been observed in up to 33% of psychiatric patients. Thus, a number of thyroid anomalies detected on routine testing spontaneously resolve so that lithium therapy may not be precluded. In this situation, monitoring thyroid function tests following each dose increase of lithium and then every 3 months after a stable dose is achieved, instead of every 6 months, is recommended.

If thyroid function is normal at baseline, it should be checked one week after the maintenance dose of lithium is achieved. If normal, thyroid function tests need be checked every 6 months. The patient should also be monitored clinically, and if he or she shows clinical signs suspicious of thyroid illness, such as cold intolerance, apathy, hair loss, or decreased energy, thyroid function tests should be checked at that time.

If at any time during the lithium therapy thyroid abnormalities are noted, consultation with the child or adolescent's primary care physician and/or an endocrinologist is recommended. It is important to determine whether or not the condition requires medical treatment. If the patient is otherwise tolerating the lithium and it is effective at treating the psychiatric disorder, it is reasonable to decide that the medication should be continued with careful monitoring of thyroid function tests and lithium levels. Fortunately, some conditions such as hypothyroidism can be treated very effectively with thyroid hormone. This is often not a major inconvenience to the family as the thyroid hormone is usually administered once a day.

All children and adolescents to be started on lithium should receive a baseline EKG, since conduction abnormalities, bradycardia, and reversible EKG anomalies have occasionally been observed in adults on lithium (Rosse et al., 1989). Therefore, although some might argue that a baseline EKG is not necessary in healthy children and adolescents, we advocate performing this relatively simple and noninvasive test so that if problems occur, comparison with a pre-medication EKG can be done. If cardiac anomalies develop, cardiology consultation is recommended prior to starting or continuing lithium therapy.

Children and adolescents treated with lithium should have a complete blood count (CBC) with a differential and platelet count checked, since lithium is known to cause a leukocytosis (Reisberg and Gershon, 1979). This leukocytosis is benign and can often be distinguished from leukocytosis caused by true infection, since during lithium therapy the neutrophilia is in the more mature forms, while infection affects the younger forms of neutrophils. It is essential that the patient and family be instructed to inform all medical professionals that their child is on lithium. They should be given a handout of lithium's side effects so

that they know that lithium can cause a leukocytosis. This may be important if the child sees a medical physician and is found to have an unexplained leukocytosis. Moreover, some medical personnel may not know that lithium causes this side effect. It is important that the patient, family, and other clinicians understand that lithium does not have to be discontinued when a leukocytosis develops.

It is very important to check electrolytes prior to initiating lithium therapy. Particular attention should be given to sodium to ensure that it is not low, since decreased sodium results in reduced excretion of lithium and can lead to lithium toxicity. The patient and family must be counseled to make sure that the child receives adequate quantities of table salt. Moreover, if the child is participating in any kind of strenuous exercise in which he or she perspires a great deal, consultation with the psychiatrist must occur and lithium levels should be monitored more frequently (see Side Effects section). The patient and family should be counseled particularly of the risks if the patient becomes dehydrated, since dehydration can result in sodium imbalance and consequent lithium toxicity.

There is some debate as to whether or not baseline EEGs should be performed on children and adolescents prior to beginning lithium. Children with conduct disorder who are treated with lithium have increased EEG abnormalities, including focal and paroxysmal changes, compared with EEGs prior to treatment (Bennett et al., 1983). EEG abnormalities did not correlate with lithium toxicity, and behavioral improvement was noted in more of the children treated with lithium than on placebo. Therefore, we do not recommend EEG as a baseline workup measure for healthy children and adolescents. However, if the child has a history of EEG disturbance, e.g., seizures and/or family history of seizure disorder, we endorse obtaining a baseline EEG and monitoring the EEG periodically thereafter.

CLINICAL PRACTICE

Dosage and Administration

Children have a greater volume of distribution and glomerular filtration rate than adults. Therefore, they necessitate an increased lithium dose per body mass. Children reach steady state faster than adults because their elimination half-life is shorter (Vitiello et al., 1988).

In children older than 12 years, the dosing of lithium is started low and gradually increased with repeated monitoring of lithium blood levels. Weller et al. (1986) devised a lithium dosage guide for children and adolescents based upon body weight, which is very useful and accurate. According to these guidelines, in a 6- to 12-year-old child, a dose of approximately 30 mg/kg/day in three divided doses will produce a lithium level of 0.6–1.2 mEq/L within 5 days (Table 8). The guide's goal is to help the clinician achieve therapeutic lithium levels of

TABLE 8 Dosing and Administration of Lithium in Children and Adolescents

Children < 12 Years: Not FDA approved Guidelines from Weller and colleagues: >25 kg initial dose on tid schedule—150/150/300; 25–40kg—300/300/300; 40–50kg—300/300/600; 50–60kg—600/300/600 Targeted therapeutic serum levels 0.6–1.2 mEq/L Should not exceed level 1.4 mEq/L Increase dose gradually monitoring efficacy versus toxicity Keep on specific dose 5–7 days Draw lithium levels 12 hours after receive medication	Children > 12 Years: FDA approved (see Indications, Table 2) Start with dose 150–300 mg/day. Check serum levels 5 days after dose. Increase gradually by 150–300 mg q 5-7 days. For acute mania doses of 1800 mg/day (level 1–1.5 mEq/L) usually required. For long-term maintenance, doses of 900–1200 mg/day are usually required yielding serum levels 0.6–1.2.
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Source: Adapted from Weller et al., 1986.

0.6–1.2 mEq/L as rapidly as possible, maximizing the efficacy of the medication and minimizing toxicity. Weller and colleagues (1986) devised this strategy after studying the effects of lithium on 10 children with bipolar disorder, manic type, and five children with conduct disorder. What is most remarkable about their study is that 13 of the 15 children achieved therapeutic lithium levels within 5 days of initiating treatment, and they suffered very few side effects, none of which required discontinuation of the medication. Lithium levels should be obtained every other day, 12 hours after the last lithium dose during this period until two consecutive lithium levels are between 0.6–1.2 mEq/L. Thereafter it is recommended that doses be adjusted gradually according to clinical efficacy versus side effects and serum lithium level. The authors do not recommend exceeding lithium levels of 1.4 mEq/L.

Alternatively, Geller and Fetner (1989) developed a lithium dosing method based on a nomogram developed from measurements of serum lithium levels 24 hours after administration of a single dose of 600 mg in children with bipolar disorder. Based on this level the subsequently administered lithium doses are determined in accordance with the nomogram of Cooper et al. (1973). This strategy was safe and useful in determining doses in 16 children with conduct disorder (Malone et al., 1995). In a study comparing the two dosing strategies, Hagino and colleagues (1998) found that the weight-based (Weller et al., 1986) and the kinetics-based (Geller and Fetner, 1989) dosing methods resulted in similar dosage estimates, with neither one avoiding side effects. The authors suggest that the two dosing strategies offer different advantages. For example, the weight-based method proposed by Weller and colleagues is a strategy that permits achieving a therapeutic level in a short time and, therefore, is more practical for inpatient settings. The intention of the kinetics-based dosing strategy is to achieve a therapeutic blood level, but the physician may adjust the dose as necessary in order to minimize side effects in an outpatient setting (Hagino et al., 1998).

It has been reported that many of the side effects of lithium that occur early during treatment including GI irritation such as nausea/vomiting and diarrhea, dizziness and confusion, muscle aches weakness, polyuria and polydipsia, and hand tremor occur when the dose of lithium is increased too rapidly so that serum lithium levels rise too quickly (Berg et al., 1974). Moreover, the lithium cation directly irritates the gastric mucosa so that taking lithium after meals will often decrease or eliminate nausea since this dose regimen slows lithium absorption. The combination of gradually increasing the lithium dose and taking the medication after meals often is successful in ameliorating GI symptoms. If the symptoms persist, switching to enteric-coated lithium such as lithobid capsules might be helpful in eliminating nausea but may exacerbate diarrhea.

Lithium blood levels should be monitored 5 days after the dose is increased. Because of their increased renal clearance, it is not uncommon for children and adolescents to require higher doses of lithium than adults, e.g., 1800 mg/day or

higher (Jefferson, 1982; Weller et al., 1986). This often achieves lithium levels of 1–1.2 mEq/L, which are necessary to control acute mania. It is believed that acutely manic patients require such high doses of lithium because while they are manic, they metabolize lithium more rapidly than when they are euthymic. This necessitates dose adjustment when the manic phase resolves, i.e., lowering the dose. Long-term maintenance therapy usually involves the administration of 900–1200 mg of lithium carbonate daily in three or four divided doses to achieve a level of 0.6–1.2 (PDR, 2001). Occasionally, children and adolescents will require higher maintenance doses to maintain adequate lithium levels. Berg and colleagues (1974) described one 14-year-old girl with bipolar disorder who required lithium doses of 2400 mg per day to reach therapeutic levels.

Because of lithium's pharmacokinetics, it is necessary to administer lithium in three to four divided doses when administered in the immediate-release form. However, when the sustained-release form is utilized, it should be given twice daily.

Lithium levels must be checked twice per week initially. When therapeutic levels are achieved, then blood levels may be monitored less frequently. After it is determined that the patient is euthymic or in remission, maintenance therapy is necessary for at least 12–18 months (Kowatch and Bucci, 1998). During this period, lithium levels should be checked at least every 3 months. We recommend checking lithium levels on a monthly basis for at least the first 3 months of the maintenance period because child and adolescent pharmacokinetics may vary depending on developmental stage. Kidney and thyroid function tests should be checked twice a year. It is important to emphasize that in contrast to adults, the National Institute of Mental Health/National Institute of Health Consensus Development Panel specifically states that there are no standards set for the prophylactic use of lithium in children and adolescents (NIMH, 1985). The decision to maintain a patient on preventative lithium therapy chronically is a clinical decision that must be made by the clinician in consultation with the patient and the patient's family.

The clinician should be aware that there is a liquid lithium preparation available, i.e., lithium citrate (see Table 7), which might be particularly helpful in younger children who have difficulty swallowing pills.

One final point regarding the dosage and administration of lithium is the utility of lithium saliva levels. Because of the difficulty in obtaining venipuncture in children, some studies have evaluated the use of saliva lithium levels (Perry et al., 1984; Vitiello et al., 1987; Weller et al., 1987). However, there is genetic variability in relating saliva to serum levels. Therefore, several serum lithium levels must first be obtained in order to interpret the saliva:serum ratio for a patient. This ratio remains fairly constant for a specific patient (Vitiello et al., 1987). However, when feasible, venipuncture is preferable for monitoring lithium levels.

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14

Anticonvulsants

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Anticonvulsants are the mainstay in the treatment of pediatric epileptic disorders (Trimble, 1990a; Dunn et al., 1998). Their use has been extended to the treatment of childhood and adolescent psychiatric disorders (Biederman et al., 1998; Connor et al., 1998) as a consequence of their documented efficacy in adult populations with bipolar illness (Bowden et al., 1994; Denicoff et al., 1997a; Keck et al., 1998; Post et al., 1998; Yang et al., 1998), aggression (Kavoussi and Coccaro, 1998) and other psychiatric disorders (Fava, 1997).

There has been a significant shift in the types of anticonvulsants employed for psychiatric treatment. In past years, phenobarbital and phenytoin were frequently the first line of anticonvulsants used, but their use in children and adolescents has been markedly curtailed because of the high incidence of associated side effects and variability in absorption. Carbamazepine (CBZ) and divalproex sodium (DVP) are now the most common anticonvulsant agents prescribed for pediatric behavioral and mood disorders. However, there remains a critical need for databased algorithms to guide anticonvulsant monotherapy and augmentation strategies in child psychiatry. An increasing knowledge of the molecular mechanisms of action of the anticonvulsants may guide future recommendations for specific clinical applications.

This chapter will focus on the application of CBZ and DVP in pediatric psychopharmacology. We will also briefly discuss some of the new generation of anticonvulsants—lamotrigine, gabapentin, topiramate and oxcarbazepine, which may add to our psychiatric armamentarium. Preliminary studies of some these “third-generation” anticonvulsants as potential mood stabilizers in adults (Calabrese et al., 1998; Kotler and Matar, 1998) have not been replicated in pediatric

populations. Nevertheless, a preliminary review of their use in psychiatry is worthwhile, as they may constitute a new wave of medications in the armamentarium of clinicians working with disabling childhood-onset neuropsychiatric disorders in children and adolescents.

CHEMICAL PROPERTIES

Carbamazepine has a structure similar to the tricyclic antidepressants (Trimble, 1990a). At a molecular level it has been described to have anticonvulsant activity, probably via inhibition of peripheral benzodiazepine receptors. There is also evidence to suggest that CBZ may inhibit α_2 -adrenergic receptors, therefore increasing the release of norepinephrine into the synaptic cleft. It may also reduce calcium influx into glial cells and block sodium channels in many brain regions as well as upregulate β - and α_1 -adenosine receptors (Shiloh and Dutt, 1999).

The structure of divalproex sodium resembles that of fatty acid. It is a simple branched-chain carboxylic acid (*n*-dipropylacetic acid) with antiepileptic activity against a variety of types of seizures (Beydoun et al., 1997). It has unique mechanisms of action (Manji et al., 1996) currently under active investigation (Chen et al., 1999a). Hypotheses about mechanisms of action include its enhancement of γ -aminobutyric acid (GABA) accumulation (Loscher, 1995) in several cerebral regions (Wolf and Tscherne, 1994; Loscher, 1995), and its interaction with voltage-sensitive sodium (Na^+) channels (Macdonald & Kelly, 1994). More recent studies show that DVP (as many other psychotropics) may ultimately regulate the expression of subsets of genes via its effects on intranuclear transcription factors, i.e., DNA-binding proteins (Chen et al., 1999b). Divalproex sodium has also been shown to play a role in the regulation of calcium (Ca^{2+}) calmodulin-dependent protein kinase activity, i.e., glycogen synthase kinase-3 β , a kinase that regulates various cytoskeletal processes, as well as the long-term gene regulation of nuclear events (Chen et al., 1999a).

INDICATIONS

For psychiatric indications for anticonvulsants, see Table 1.

Carbamazepine is approved for the prophylactic treatment of partial seizures with complex symptomatology (psychomotor or temporal lobe seizures), generalized tonic-clonic (grand mal) seizures, and trigeminal neuralgia in adults in the United States (American Hospital Formulary Service, 1996). Carbamazepine has been widely used to treat a variety of off-label psychiatric conditions in adults. In a comprehensive survey conducted by Denicoff and colleagues (1994), CBZ was reportedly used for mania, bipolar depression, intermittent explosive disorder, schizo-affective disorder, pain syndromes, posttraumatic stress disorder, borderline personality disorder, unipolar depression, schizophrenia, and

TABLE 1 Psychiatric Indications for Anticonvulsants

Established Indications:
Bipolar disorder in adults
Alcohol withdrawal
Chronic pain/pain associated with nerve injury
Possible Indications:
Bipolar disorder in children and adolescents
Major depression
Episodic dyscontrol syndrome
ADHD
Conduct disorders
Psychotic disorders as adjunct
Functional enuresis
Sleep terror disorder

alcohol withdrawal. It is not approved for the treatment of psychiatric disorders in children. Case series have suggested efficacy in conditions such as conduct disorder (CD) (Kafantaris et al., 1992) and attention-deficit hyperactivity disorder (ADHD) (Silva et al., 1996). Additional use of CBZ suggests efficacy for the treatment of mania in children with bipolar disorder (BPD) (Kowatch and Bucci, 1998).

Divalproex sodium is an anticonvulsant approved for treating adults with simple and complex absence seizures (Mattson et al., 1992). It has shown efficacy across a broad spectrum of BPD subtypes (i.e., pure mania, mixed mania, and rapid cycling) (Pope et al., 1991; McElroy et al., 1992; Calabrese et al., 1993; Bowden et al., 1994). Case series (Papatheodorou and Kutch, 1993; West et al., 1994; Papatheodorou et al., 1995) suggest that DVP may be effective and well tolerated in acutely manic adolescents, however its therapeutic success as monotherapy is uncertain. Preliminary uncontrolled studies also suggest that DVP may play a role in the management of behavioral dyscontrol (Guay, 1995) among adults (Sovner, 1991) and adolescents (Kastner and Friedman, 1992) with comorbid BPD and mental retardation. It has also been used off-label in the treatment of pathologic aggression in patients with dementia, organic brain syndrome, psychosis, and personality disorders (Stein et al., 1995).

Bipolar Disorder

There is a lack of controlled studies in children or adolescents with mood disorders (Campbell and Cueva, 1995; Kowatch and Bucci, 1998) for both CBZ and DVP. Many open and controlled trials have shown CBZ's efficacy in the acute

(Brown et al., 1989; Okuma et al., 1990) and prophylactic (Stuppaeck et al., 1990; Greil and Kleindienst, 1999a) treatment of adults with BPD Type I (Greil and Kleindienst, 1999b) and BPD Type II disorder (Greil and Kleindienst, 1999a). The majority (Denicoff et al., 1997; Greil et al., 1997), but not all (Lusznat et al., 1988; Stuppaeck et al., 1990), studies have shown CBZ to have comparatively less efficacy than lithium in the prophylaxis of mania (Sharma et al., 1997). Increased severity of mania, rapid cycling, and poor responses to lithium have been described as predictors of improved response to CBZ (Post, 1987). Off-label uses of CBZ suggest efficacy for the treatment of mania in children with BPD (Kowatch and Bucci, 1998).

Divalproex sodium has been reported to have acute antimanic properties (Bowden et al., 1994) in at least six controlled studies of adults with BPD (Post et al., 1996). There is a paucity of controlled data for the use of DVP in children with psychiatric disorders. Kowatch and colleagues (R. Kowatch, personal communication, March 1999) recently completed an open randomized trial of mood stabilizers in children with type I and type II BPD. Forty-two children and adolescents (mean age 11.4) diagnosed with BPD were treated with DVP, lithium, or CBZ in a single-blind open randomized 6-week trial. The investigators found no significant differences between the groups at the completion of the study. On intent-to-treat analysis, DVP showed a 46% response rate, lithium 34%, and CBZ 34%. Eighty-five percent ($n = 11$) of 13 subjects receiving a mood stabilizer combined with a stimulant showed a therapeutic response to this combination during the continuation phase. Stimulants were used to treat residual hyperactivity and inattention in BPD cases.

Strober and colleagues (M. Strober, personal communication, March 1999) recently completed a historical case-control comparison between lithium and DVP in adolescents with mixed mania. Twenty-four lithium historical case controls were compared to 16 subjects treated with DVP. Both groups showed a steady and comparable decline in symptom severity during the acute phase of the study, lasting 4 weeks. However, the probability of remaining well by year 3 was approximately 80% for DVP compared to 50% percent for lithium. While not statistically significant, there was a two-fold increase in the hazard of relapse in subjects treated with lithium compared with subjects on DVP. Generally, lithium was better tolerated than DVP in this cohort, but there was no difference in discontinuation rates due to side effects.

These are two of the few (Licamele and Goldberg, 1989) prospective controlled studies of mood stabilizers conducted in children and adolescents with BPD showing a potential efficacy for DVP, especially in combination with stimulants. Investigators have emphasized that the mood disturbance in this population does not overlap with the ADHD symptoms (Wozniak and Biederman, 1996; Faraone et al., 1997), an area that clearly deserves controlled studies. This has treatment implications since after appropriately addressing the mood disorder,

residual ADHD symptoms may require treatment with stimulants (Wozniak and Biederman, 1996).

Major Depressive Disorder

Carbamazepine's antidepressant efficacy in adults (Okuma et al., 1981; Post, 1990; Stuppaeck et al., 1994) has been shown to be weaker than its antimanic effects (Denicoff et al., 1994). No controlled studies of the treatment of pediatric depression with CBZ have been reported so far. In one prior open study, Groh (1976) studied 62 nonepileptic children with abnormal behaviors and found that the majority of the 27 patients who showed improvement had a "dysphoric or dysthymic syndrome" characterized by irritability and mood lability suggestive of depression. In addition, one literature review determined that positive results were seen in children treated with CBZ for the target symptoms of dysphoria (Remschmidt, 1976).

The treatment of childhood refractory depression is an area that deserves controlled studies. Children with depressive disorders ("unipolar depression") often present with symptoms of irritability and depression. Unfortunately, diagnostic clarification too frequently follows induction of mania secondary to antidepressant treatment (Geller et al., 1993). Given that antidepressant-induced mania may be a marker for increased vulnerability to antidepressant-induced cycle acceleration among adult treatment-refractory bipolar patients (Altshuler et al., 1995), it is likely that depressed children may represent a high-risk population (Geller et al., 1993). Clinicians often face a dilemma when prescribing antidepressants for children with a family history of mood disorders or paternal alcoholism. Pharmacotherapy with mood stabilizers in combination with an antidepressant may conceivably have a preferable long-term outcome in children with refractory depression as in some adult rapid-cycling patients (Post et al., 1997), although this remains to be systematically studied.

Aggression and Conduct Disorder

The treatment of chronic or intermittent severe aggression with pharmacological agents in children and adolescents continues to be unsatisfactory (Connor et al., 1998). Several drugs are postulated to be effective for the treatment of aggression in children (Kruesi et al., 1992), nonetheless, the treatment of aggression in children with anticonvulsants remains empiric and tentative due to lack of controlled data (Sporn and Sachs, 1997). Moreover, many of the studies on adult aggressive populations have allowed the use of concomitant medications, making the identification of a dependent effect specific for the drug under study (Fava, 1997) difficult to infer for pediatric use. Agents such as CBZ and DVP may be potentially useful in the chronic management of aggressive behavior (Pabis and Stanislav, 1996), particularly in patients with abnormal EEG findings. However, the efficacy

of these drugs in patients with and without a seizure disorder remains to be established.

Some of the first clinical observations about CBZ in nonepileptic children were noted by Trimble and Corbett (1988), who found that higher serum levels of CBZ, i.e., 8–12 $\mu\text{g}/\text{mL}$, were associated with decreased behavior problems in children. Previously, in a double-blind, placebo-controlled crossover trial, Groh (1976) reported significant improvement in “a multitude of behavior problems” in 20 children and adolescents with CD treated with CBZ. Years later, in an open pilot study in hospitalized children, Kafantaris and colleagues (1992) reported significant declines in aggressiveness and explosiveness in 10 children (mean age 8.2 years) diagnosed with CD after 3 weeks of treatment with CBZ. Nonetheless, a more recent controlled study did not replicate these data (Cueva et al., 1996). Using a parallel-group, double-blind, placebo-controlled design, Cueva and colleagues (1996) treated 22 hospitalized children, aged 5–12 years, diagnosed with CD with CBZ for 6 weeks. Carbamazepine was not superior to placebo at an optimal mean daily dose of 683 mg, with serum levels of 4.98–9.1 $\mu\text{g}/\text{mL}$. Untoward effects associated with administration of CBZ were common. A replication of this study is necessary to define the role of CBZ in the treatment of aggression and CD in children and adolescents.

Unlike CBZ treatment, this day there is no controlled studies published for the treatment of CD with DVP.

Aggression and Intermittent Explosive Disorder

In daily clinical practice, the diagnosis of intermittent explosive disorder (IED) frequently describes a group of children who do not satisfy criteria for ADHD or CD or BPD and yet present with severe disruptive behaviors. Improvement on CBZ has been described for children with behavioral disorders who may coincide with this diagnosis (Kuhn-Gebhart, 1976), especially among those with abnormal EEGs. In 1976, Remschmidt (1976), in a comprehensive review of the literature, concluded that clinical improvement was found for aggressive/hyperaroused behavior disorders treated with CBZ. Puente (1976) treated 46 intermittently aggressive children with CBZ (average dose 300 mg/day with a range of 100–600 mg/day given for a mean duration of 3 months) and observed significant improvement in 70% of them.

Even fewer data are available for DVP. Recently, some practitioners have begun to use DVP to treat intermittent explosiveness in both adults with dementia and organic brain syndrome (Fava, 1997; Wroblewski et al., 1997). Evidence for the efficacy of DVP in adolescents with IED is suggested by a 5-week open trial of DVP in 10 adolescents with chronic temper outbursts and mood lability which showed improvement in temper outburst frequency and mood swings severity on

clinical outcome measures in all subjects (Donovan et al., 1997). These data must be regarded as preliminary, and further studies are needed.

Attention Deficit Hyperactivity Disorder

There is preliminary evidence that CBZ may have efficacy in the treatment of children with symptoms of hyperactivity (Remschmidt, 1976). In 1996, Silva and colleagues published a meta-analysis of the world literature of children with ADHD features treated with CBZ. Seven open studies and three double-blind placebo-controlled studies showed a significant therapeutic response. Despite these encouraging data, CBZ is still considered to be a third- or fourth-line agent for the treatment of ADHD. Plasma levels, which need to be measured periodically, are not correlated with clinical improvement in ADHD (Evans et al., 1987). Carbamazepine has not been directly compared to stimulants, antidepressants, or clonidine in the treatment of ADHD. An equivalency study merits to be done in children refractory to standard stimulant therapy.

Unusual Indications

Unusual off-label uses for CBZ and DVP are listed in Table 1 (e.g., psychotic disorders as adjunct, enuresis, sleep terror) and will not be discussed in detail in the text. There is a dearth of controlled data to support their use in child and adolescent psychiatry, and their use remains highly empiric.

CONTRAINDICATIONS

Contraindications to CBZ are listed in Table 2. Contraindications to DVP are listed in Table 3. Relative contraindications for the use of DVP in children are age <6 years, uncontrolled medical illness, and coadministration with clonazepam.

TABLE 2 Contraindications for Carbamazepine Use

Absolute:
Known hypersensitivity to carbamazepine or tricyclic antidepressants
History of bone marrow depression
On MAOI within past two (2) weeks
Pregnancy
Relative:
Liver disease
Kidney disease

TABLE 3 Contraindications for Valproic Acid Use

Absolute:
Known hypersensitivity to valproic acid or related drug
History of bone marrow depression
Pregnancy
Relative:
Liver disease
Kidney disease

SIDE EFFECTS

Carbamazepine has been shown to be well tolerated as long-term monotherapy compared to phenobarbital, phenytoin, or DVP in children with epilepsy or febrile convulsions (Herranz et al., 1988) or to phenobarbital and phenytoin in adult patients with epilepsy (Keranen and Sivenius, 1983). Nevertheless, multiple side effects have also been described in pediatric studies (Table 4). A comparison of the adverse effect profile in the Kowatch's sample (R. Kowatch, personal communication, March 1999) shows that nausea (46%), rash (8%), and dizziness (8%) were more prevalent in youngsters taking CBZ than in children on DVP, who experienced overall less nausea (20%), rash (0%), and dizziness (0%). Sedation

TABLE 4 Side Effects of Carbamazepine

Common:
Diplopia
Drowsiness
Incoordination
Nystagmus
Nausea
Leukopenia
Skin rashes
Uncommon:
Agranulocytosis and aplastic anemia
Hyponatremia and water intoxications
Liver toxicity
Neurotoxicity
Mania
Exacerbation/precipitation of behavior problems
Hypocalcemia
Effects on male reproductive systems?

(20%) was the only more common (not significant) side effect for DVP than for CBZ (15%).

Neurological side effects were considered the most common potential adverse effects for CBZ in an extensive review of the subject (Seetharam and Pellock, 1991). Idiosyncratic effects include hepatic and hematological hypersensitivity reactions. A benign leukopenia may occur in 10% of adults and children and appears to be unrelated to aplastic anemia, which may occur in approximately 1 in 575,000 treated patients per year (Seetharam and Pellock, 1991).

Neurotoxicity: Diplopia

Diplopia is a common side effect of CBZ, which often remits spontaneously or after the dose is decreased (Menkes, 1990). Both phenytoin and CBZ can affect retinal function, whereas DVP reportedly does not (Bayer et al., 1995). Glare sensitivity may be the chief complaint from patients treated with CBZ, and the clinician should develop office-screening methods to improve the sensitivity for detection of this potential side effect before referral to a specialist.

Neurotoxicity: EEG Worsening

Carbamazepine can exacerbate seizures and/or worsen the EEG, precipitate status epilepticus (Menkes, 1990), or, rarely, induce a continuous, nonepileptic myoclonus in children and adolescents (Snead and Hosey, 1985). Most recently, Parmeggiani and colleagues (1998) described 10 new cases of children with epilepsy, (6 on polytherapy) in which seizure frequency was increased ($n = 9$) and new seizures appeared ($n = 8$), mostly absences. Electroencephalographic recordings showed slowing background activity, increased paroxysmal abnormalities, and/or diffuse/generalized spike waves shortly after introduction of CBZ at therapeutic doses but below therapeutic CBZ plasma concentrations (Parmeggiani et al., 1998). Cognitive function worsened in eight of these cases (Parmeggiani et al., 1998). After CBZ withdrawal, clinical and EEG improvement was evident in a few days (Parmeggiani et al., 1998). Likewise, Pleak and colleagues (1998) observed that two 11-year-old boys who were treated with CBZ developed sharp waves and spike abnormalities on their EEGs. The underlying pathogenetic mechanism of EEG worsening with CBZ is not clearly understood. However, the pathophysiology of seizure exacerbation may conceivably be related to behavioral disturbances and cases of CBZ-induced mania.

Drowsiness, incoordination, vertigo, and nystagmus are also potential but transient side effects of CBZ (Menkes, 1990). Slurred speech, dystonic reactions, muscle rigidity and tinnitus may occur occasionally (Trimble, 1990a). When CBZ is given with other drugs such as diltiazem, verapamil, erythromycin, isoniazid, propoxyphene, and alcohol, neurotoxicity can be induced (Macphee et al., 1986).

Congenital Malformations; Neural Tube Defects

Congenital malformations constitute some of the most serious side effects in newborns of women taking CBZ. Persistent vomiting and transient hypotonia/hypertonia with intermittent opisthotonos have been noticed in newborns of mothers treated with CBZ (Kaymemb et al., 1997). Caution should be exercised in female adolescents receiving anticonvulsants. All women of childbearing age should receive a detailed history and pregnancy test, if necessary, before starting CBZ or DVP.

Exacerbation of Aggression, Irritability, Impulsivity, and Other Behaviors

Aggravation and/or precipitation of behavioral problems, including hyperactivity, mania (Pleak et al., 1988), depression, and suicidal ideation (Brent et al., 1986) attributed to antiseizure medication in children with epilepsy has been described with benzodiazepines, DVP, gabapentin, phenobarbital, vigabatrin (Wallace, 1996), and CBZ (Pleak et al., 1988). Children with concomitant ADHD would appear to be at higher risk for these secondary side effects (Dulac et al., 1991).

Increased irritability, mood lability, tantrums, and disruption of normal sleep patterns have been described for CBZ in the treatment of children and adolescents with conduct disorders and hyperactivity (Evans et al., 1987). These symptoms often resemble the target symptoms or suggest mania induction, a phenomenon specifically described for CBZ (Reiss and O'Donnell, 1984; Pleak et al., 1988). Discontinuation (or quick taper) of the medication is indicated. If remission of abnormal behavior occurs shortly (24 hr) after discontinuing the medication, the clinician may consider the phenomenon secondary to the medication. If severe irritability and mood lability persist for more than 2 or 3 days after discontinuation of the medication, the induction of mania can be suspected. The use of behavior rating scales, which may help elucidate whether or not the drug is helping or hindering therapy, is recommended. For an excellent review of the subject of disinhibition in children and adolescents with psychiatric disorders, the reader is referred to Wilens and colleagues (1998).

Skin Rashes

Rashes are relatively common with CBZ use (Pellock, 1987). Pellock observed rashes in 5% of a sample of children treated with CBZ (Pellock, 1987). Nonetheless, severe skin rashes secondary to CBZ are rare (Trimble, 1990a). Patch testing may be useful in the detection or confirmation of exanthematous eruptions caused by CBZ (Liao et al., 1997).

Lipids

In a recent study of ($n = 23$) children with epilepsy treated with CBZ for 1.5 years or DVP ($n = 16$) for 1.3 years, the patients receiving CBZ had significantly higher mean serum total cholesterol (TC) levels, mean low-density lipoprotein level, and mean TC/high-density lipoprotein ratio than controls (Sozuer et al., 1997). Serum lipids in patients receiving DVP were not significantly different from the control group mean (Sozuer et al., 1997). The authors concluded that long-term prospective studies were necessary to determine whether chronic CBZ therapy was a risk factor for atherosclerotic disorders. Conversely, an increase in serum high-density lipoproteins was reported in a smaller sample of 21 patients treated with CBZ and therefore interpreted as a possible protective factor against atherosclerosis (Yalcin et al., 1997).

Hematological Side Effects: Leukopenia

Leukopenia is a very common side effect of CBZ treatment (Pellock, 1987). Pellock (1987) reported a nonprogressive leukopenia of less than $4000/\text{mm}^3$ in approximately 13% of a sample of 220 children below the age of 16 and of less than $3000/\text{mm}^3$ in 2.3% of the sample. Spontaneous reversal of blood counts was seen in 75% of the children. Similarly, in a series of 176 children with epilepsy treated with CBZ, 8.0% and 17.0% of the children developed leukopenia and neutropenia, respectively, over a 12-month period (Evans et al., 1989). Rarely, CBZ-induced leukopenia progresses to agranulocytosis or aplastic anemia, which is a medical emergency (see below).

Agranulocytosis and Aplastic Anemia

Agranulocytosis and aplastic anemia are uncommon but potentially very serious, life-threatening side effects of CBZ therapy (Ueda et al., 1998). The clinician should monitor for bruising, bleeding, sore throat, fever, lethargy, and mouth ulcers accompanied by a precipitous drop in white blood cell count (Trimble, 1990a). This necessitates prompt medical attention and consultation with a hematological specialist. A drop in the granulocyte count to less than 1000 requires that the medication be gradually tapered and discontinued (Trimble, 1990a). These effects are usually reversible, but because death has been reported in 1 per 50,000 cases, caution is advised (Trimble, 1990a). Blood counts should be monitored at least every 6 months during treatment with CBZ (see Initiating and Maintaining Treatment section).

Blood Dyscrasias

Neutropenia and thrombocytopenia are uncommon side effects of CBZ and DVP therapy (Trimble, 1990a). Thrombocytopenia is often transient, and although

dose related (Barr et al., 1982) and perhaps autoimmune (Menkes, 1990), it may not require reduction or discontinuation of the drug (Barr et al., 1982). It should be noted, however, that infection could aggravate the thrombocytopenia, resulting in bruising and minor bleeding (Barr et al., 1982).

A recent cohort study conducted by Blackburn and colleagues (1998) investigated the frequency of blood dyscrasias (neutropenia, agranulocytosis, hemolytic anemia, thrombocytopenia, pancytopenia, or aplastic anemia) in a total of 29,357 patients, ages 10–74 years, taking CBZ, DVP, phenobarbital, or phenytoin. Eighteen cases of serious blood dyscrasia considered to have a temporal relationship to drug use were reported (Blackburn et al., 1998). Of these cases, 7 were taking two or more drugs. The overall rate of blood dyscrasias was 3–4/100,000 prescriptions, and rates did not differ among the four drugs. All except one patient recovered (Blackburn et al., 1998).

Hyponatremia and Water Intoxication

Since CBZ stimulates the release of antidiuretic hormone (ADH), it can cause the syndrome of inappropriate antidiuretic hormone release (SIADH) characterized by hyponatremia, water intoxication, lethargy, headache, nausea/vomiting, edema, seizures, and very rarely acute renal failure (Trimble, 1990a). These effects may be more likely to occur when lithium and CBZ are used concomitantly.

Liver Toxicity

Liver toxicity is a rare side effect of CBZ therapy (Trimble, 1990a). Camfield and colleagues found that 9% of children on CBZ had mildly elevated aspartate aminotransferase levels (1985).

Effects on Male Reproductive Systems

Recent investigation in adults found that CBZ, valproate, and oxcarbazepine may have effects on the male reproductive system (Rattya et al., 2001). Endocrine function was measured in 21 males on monodrug therapy with valproate, 40 males on CBZ, and 29 on oxcarbazepine for epilepsy as compared to 25 healthy male controls. Twelve of the 21 (57%) males taking valproate had increased serum androgen levels. High androstenedione levels were also observed in males taking valproate. Males with increased androgen levels on valproate were significantly more obese than males receiving valproate, who had normal serum androgen concentrations. Dehydroepiandrosterone sulfate concentrations were low in males on CBZ, whereas sex hormone-binding globulin serum levels were high. The effects of oxcarbazepine may be dose-dependent (Rattya et al., 2001).

While sex hormone concentrations were normal in males on doses of <900 mg/day of oxcarbazepine, serum levels of testosterone, gonadotropins, and sex hormone-binding globulin were significantly increased in males taking 900 mg/day or higher doses of oxcarbazepine.

One of 21 males (5%) on valproate experienced decreased sexual functioning as compared to 7 of 40 (18%) on CBZ and 5 of 29 (17%) on oxcarbazepine (Rattya et al., 2001). In contrast, some males reported improved sexual functioning: 4 of 21 patients (19%) on valproate, 3 of 40 patients (8%) on CBZ, and 1 of 29 patients on oxcarbazepine.

Serum insulin levels were significantly increased in patients on CBZ, valproate, and oxcarbazepine (Rattya et al., 2001). These levels were highest in patients on valproate. There are no data in children. Further study in pediatric populations is clearly warranted.

Side Effects of Divalproex Sodium

In a multicenter trial of DVP monotherapy in patients with poorly controlled partial epilepsy randomly assigned to a "high" (80–150 µg/mL; 555–1040 µmol/L) versus a "low" (25–50 µg/mL; 175–345 µmol/L) plasma level group, tremors, thrombocytopenia, alopecia, asthenia, diarrhea, vomiting, and anorexia were significantly more frequent in the high serum level group compared to the low serum level group (Beydoun et al., 1997) (Table 5).

TABLE 5 Side Effects of Valproic Acid

Common:
Gastrointestinal upset
Increased appetite/weight gain
Sedation
Tremor
Uncommon:
Liver toxicity
Hyperammonemia
Blood dyscrasias
Alopecia
Decreased serum carnitine
Neural tube defects
Pancreatitis
Hyperglycinemia
Menstrual irregularity
Effects on male reproductive systems?

Tremor

Tremor, but not asterixis (Bodensteiner et al., 1981), can be a common side effect of DVP, a drug considered to have minimal overall adverse effects (Trimble, 1990b). In a comparison with CBZ-induced tremor (22%), DVP-induced tremor (45%) was significantly more common in a large ($n = 480$) sample of adults with complex partial seizures or generalized tonic-clonic seizures (Mattson et al., 1992). Divalproex sodium-induced tremor appears to be dose-related; it does not abate with continued treatment, but may respond to a lowering of the dosage.

Alopecia

Hair loss has been considered an uncommon side effect of DVP therapy (Trimble, 1990a). Recent reports however, recognize pediatric alopecia [distinct from toxic alopecias, a form of diffuse but total hair loss (Uehlinger et al., 1992)] as one of the more common (14%) dose-related side effects specific to DVP (Devilat et al., 1991). It usually does not abate with continued treatment but may respond to a lowering of the dosage. Obviously, clinicians may be reluctant to lower medication dosage if therapeutic benefits may be compromised. Symptomatic management of alopecia includes trace mineral supplementation (zinc and multivitamins), treatment with minoxidil, and hair replacement pieces (McKinney et al., 1996).

Neurotoxicity

Divalproex sodium reportedly has minimal neurological adverse effects (sedation, ataxia, impairment of cognitive function) compared with other antiepileptic drugs (Davis et al., 1994). Neural tube defects, predominantly spina bifida—at a risk of 1–2%—is potentially the most serious neurological side effect associated with maternal use of DVP. The coadministration of DVP and clonazepam can precipitate status epilepticus (Trimble, 1990a).

Sedation

Most anticonvulsants can cause drowsiness (Wallace, 1996). Sedation is considered to be a common potential side effect of DVP therapy. Avoiding polydrug therapy (Trimble, 1990a) can reduce its incidence. In Kowatch and collaborator's study of anticonvulsants in children with BPD (R. Kowatch, personal communication, March 1999), sedation (20%) among children taking DVP was a common side effect for DVP compared to CBZ (15%). Divalproex sodium-induced sedation tends to be self-limited (Bourgeois, 1988).

Gastrointestinal Upset

Gastrointestinal side effects are common side effects encountered in patients receiving DVP (Wilder et al., 1983). Nausea, stomach cramps, and diarrhea were

among the most frequent adverse effects reported in a study of adults with rapid-cycling BPD treated with DVP (Calabrese et al., 1992). Taking an enteric-coated preparation (e.g., Depakote®), with food/formula could help minimize stomach upset.

Increased Appetite/Weight Gain

Increased appetite may be a significant side effect of DVP, particularly for responders (Menkes, 1990) who may be receiving enteric-coated medication. The potential increase in weight gain in girls treated with DVP or CBZ before and during puberty was recently studied by Rattya and collaborators (Rattya et al., 1999). A sample of 87 girls including 40 girls 8–18 years old taking DVP and 19 girls taking CBZ, were compared with 49 healthy controls cross-sectionally and longitudinally for growth analysis. None of the anticonvulsants affected linear growth or pubertal development in girls with epilepsy (Rattya et al., 1999). However, on clinical examination an increase in relative weight was seen in girls treated with DVP compared to controls (Rattya et al., 1999). This adverse effect was seen in girls who started their medication before as well as during puberty (Rattya et al., 1999). Conversely, patients taking CBZ had similar weights compared to controls. Neither DVP nor CBZ affected fasting serum insulin during the period of exposure (average 2.8 and, 4.1 years, respectively) (Rattya et al., 1999). This interesting study suggests that DVP-related weight gain seen pre-pubertally in girls with epilepsy may not be associated with hyperinsulinemia (Rattya et al., 1999).

Liver Toxicity

Transient and nonprogressive DVP dose-related increases in liver function tests (i.e., raised serum alkaline phosphatase and transaminase values) have been described in 44% of patients treated with this agent (Menkes, 1990). Dose reduction is often therapeutic for this phenomenon. Conversely, fatal hepatotoxicity, a more rare, idiosyncratic occurrence associated with DVP, appears to be unrelated to drug dosage (Bryant and Dreifuss, 1996). According to a retrospective study of fatal hepatotoxicity associated with DVP, over one million patients received new prescriptions for DVP during the years 1987–1993, and only 29 patients developed fatal hepatotoxicity (Bryant and Dreifuss, 1996). Decreased alertness, jaundice, vomiting, and increased seizures were some of the most common presenting signs (Bryant and Dreifuss, 1996).

The incidence of fatal hepatic failure associated with DVP therapy is highest in children under the age of 3 years (Appleton et al., 1990), particularly in children with mental retardation receiving anticonvulsant polytherapy or children with developmental delay (Appleton et al., 1990). The pathogenesis of DVP hepatotoxicity is unclear but may be related to the accumulation of a toxic metabolite of DVP impairing fatty acid oxidation (Appleton et al., 1990), especially in pa-

tients with coincident metabolic disorders (Bryant and Dreifuss, 1996). Patients younger than 2 years old receiving DVP as polytherapy are at a very high risk (1:600) of developing this complication (Bryant and Dreifuss, 1996). A panel of experts has recently recommended therapeutic oral L-carnitine supplementation for this group in dosage of 100 mg/kg/day, up to a maximum of 2 g/day (De Vivo et al., 1998).

Menstrual Irregularity

Menstrual irregularity has been considered an occasional adverse effect of DVP therapy. Recent concerns about DVP's potential for causing polycystic ovaries (PCO) in adolescents originated from a report by Isojarvi and colleagues (Isojarvi et al., 1993). Hyperandrogenism and chronic anovulation in the absence of identifiable adrenal or pituitary pathology characterizes this highly prevalent syndrome, affecting 2–22% of women in the general population (Chappell et al., 1999). In a sample of 98 women with epilepsy (mean age 33), Isojarvi and colleagues (1998) found that 12 of 29 women (43%) taking DVP alone and 11 out of 49 (22%) taking CBZ had PCO diagnosed with vaginal ultrasonographies and serum hormone concentrations. Eighty percent of the DVP group had started treatment prior to age 20. The association of obesity and hyperinsulinemia with possible DVP-related PCO was later postulated by this group (Isojarvi et al., 1998) and other physicians (Irwin and Masand, 1998; Eberle, 1998). Most of the patients reported in this series were obese, which supposedly would have led to insulin resistance and subsequent hyperstimulation of the ovaries, hyperandrogenism, and PCO. None of the women taking CBZ were described as severely obese, making the mechanism of action of CBZ-induced PCO somewhat unclear.

Comparable reports have not appeared in the psychiatric literature. A recent report by Murialdo and colleagues (1997) suggests that the prevalence of PCO (16.9%)—but not of multifollicular ovaries—in 101 women with epilepsy (aged between 16 and 50 years) is not higher than those reported in the general population. However, adult and adolescent women with epilepsy treated with DVP may have increased testosterone and androstenedione levels and a higher luteinizing hormone/follicle-stimulating hormone ratio in the luteal phase (Murialdo et al., 1998), making a distinction between independent variables difficult to make. Until more specific guidelines are available, female adolescent patients taking DVP should be carefully monitored for early signs of menstrual irregularities or hirsutism.

Withdrawal Seizures

Withdrawal seizures can occur in patients without a past history of seizure disorder (Menkes, 1990). They are considered equally rare for CBZ, DVP, and phenytoin (Duncan et al., 1989). Nonetheless, a recent article by Chadwick and colleagues (1999) suggests a comparatively lower rate of seizure recurrence for

pediatric and adult patients in remission of epilepsy undergoing CBZ treatment compared to phenobarbitone/primidone, phenytoin, or DVP. Withdrawal seizures in general are seen primarily with barbiturates and benzodiazepines.

Unusual Side Effects of DVP

Hyperammonemia, hypocalcemia, pancreatitis (Bourgeois, 1988), hyperglycemia (Gram and Bensten, 1985), and lower than normal prothrombin time and platelet counts (Devilat and Blumel, 1991) are all unusual potential side effects of DVP therapy. Previous reports of hyperammonemia commonly seen in patients treated with DVP (Menkes, 1990) have not been replicated. Elevated fasting ammonia levels in asymptomatic patients receiving therapeutic dosages of DVP do not necessitate discontinuation of the drug since there is no correlation between increased ammonia levels and liver failure (Laub, 1986). However, this may play a role in the development of stupor (Coulter and Allen, 1980).

Overdose/Toxicity

Carbamazepine toxicity is manifested by drowsiness, nausea/vomiting, gait disturbance, nystagmus, confusion, neuromuscular excitability, and seizures (Menkes, 1990). Peak toxic levels may not occur until the second to third day postingestion due to its slow absorption (Arana and Hyman, 1991). Overdose with CBZ can be lethal (Arana and Hyman, 1991). In a retrospective study of 307 patients, 41 (13%) had a fatal outcome (Schmidt and Schmitz-Buhl, 1995). Doses exceeding 24 g were important indicators of fatality, whereas cardiac arrhythmias and other cardiovascular complications were rare (Schmidt and Schmitz-Buhl, 1995). The course of intoxication in this sample appeared to be more benign in patients younger than 15 years (Schmidt and Schmitz-Buhl, 1995). The management of CBZ overdose is primarily supportive, to prevent potential AV block (Arana and Hyman, 1991), possible respiratory depression (Schmidt and Schmitz-Buhl, 1995), stupor, and coma. Hemodialysis is not therapeutic (Arana and Hyman, 1991).

Drowsiness, weakness, incoordination, and confusion indicate divalproex sodium toxicity (Trimble, 1990a). Treatment is also supportive, requiring hospitalization.

Side effect profiles for phenytoin and phenobarbital are shown in Tables 6 and 7.

PHARMACOKINETICS

For pharmacokinetic properties of anticonvulsants, see Table 8.

Generally, consideration of standard pharmacokinetics in children and adolescents and the guidelines established in treating epilepsy are utilized (Dreifuss

TABLE 6 Side Effects of Phenytoin

Common:
Hirsutism
Gum hypertrophy
Folate deficiency
Psychomotor retardation
Uncommon:
Encephalopathy (“Dilantin dementia”)
Altered vitamin D/calcium metabolism
Biotin deficiency
Vitamin E deficiency
Liver toxicity
Neurotoxicity
Hypersensitivity reaction
Coarsening of facial features
Headache
Gynecomastia
Hyperglycemia

and Langer, 1987). Prepubertal children may metabolize anticonvulsants more rapidly than adolescents (Perucca, 1995) and may require higher and more frequent doses than adolescents (Trimble, 1990a).

Carbamazepine is slowly absorbed from the GI tract, and peak plasma concentrations are achieved in 2–8 hours following oral administration. The usual maintenance dose is 10–20 mg/kg/day, administered in divided doses (bid or tid) given CBZ’s short half-life after autoinduction.

Carbamazepine has linear kinetics so that a dose increase will result in a predicted increase in serum blood levels (Trimble, 1990a). It requires a relatively slow titration, starting at 100 mg once or twice daily in preadolescents, due to

TABLE 7 Side Effects of Phenobarbital

Depression
Mood changes
Suicidal ideation
Paradoxical behavior rebound/ worsening
Hyperactivity
Cognitive impairment
Drowsiness

TABLE 8 Pharmacokinetic Properties of Anticonvulsants

Drug	Elimination	Protein binding (%)	Half-life (hr)	Desired serum level ($\mu\text{g/mL}$)
Carbamazepine	Hepatic	40–90	12	8–12
Valproic acid	Renal	95	8–20	50–125
Topiramate	Metabolized ^a	15 ^c	11–22 ^c	Not established ^d
Gabapentin	Renal ^b	6 ^a	5–7 ^c	Not established ^d
Lamotrigine	Metabolized ^a	55 ^c	30 ^a	Not established ^d

^a From: Kilpatrick, 1999.

^b From: Curry and Kulling, 1998.

^c From: Bourgeois, 2000.

^d From: Epilepsy Foundation of America, Inc. Medical Therapy, 2000. <http://206.239.147.40/clinicalcare/treatment/medicaltherapy.html>

the possibility of described somatic and cognitive adverse effects (Pulliainen and Jokelainen, 1994). In the course of a few weeks CBZ is expected to autoinduce its cytochrome-metabolizing enzymes in the liver (Cepelak et al., 1998), mainly CYP3A4 (Ketter et al., 1995), resulting in decreased serum level. Carbamazepine half-lives may average 12 hours during chronic administration in adolescents due to CBZ's autoinduction properties. Although therapeutic plasma levels for children with mood disorders have not yet been determined, plasma concentrations for anticonvulsant effect are in the range of 4–14 $\mu\text{g/mL}$. Plasma levels should be obtained 2–4 days after achieving steady-state plasma concentration. Carbamazepine and DVP are highly bound to protein (over 90%) (Trimble, 1990a). When protein-binding capacity is altered, marked changes in the free fractions can happen.

The bioavailability of the DVP enteric-coated capsule is 90% with peak levels occurring 4 hours after dose, and the bioavailability of the oral valproate capsule is 93%, with peak levels occurring 1–2 hours after dose (Zaccara et al., 1988). The peak time for both formulations is delayed by food (Zaccara et al., 1988). Steady-state plasma levels of DVP are attained in 2–4 days (Zaccara et al., 1988). The volume of distribution is 0.26 L/kg in children and 0.19 L/kg in adults. The clearance is 0.027 L/hr/kg in children and 0.0066 L/hr/kg in adults. The half-life is 7.2 ± 2.3 hours in children and 13.9 ± 3.4 hours in (healthy) adults (Levy et al., 1984).

DRUG INTERACTIONS

For drug interactions, see Tables 9–11.

The multiple cytochrome P450-mediated potential drug interactions of CBZ and DVP are not covered in detail in this textbook. For a comprehensive

TABLE 9 Anticonvulsant Drug Interactions

Anticonvulsant Effects Increased by:

- Cimetidine
- Chloramphenicol
- Chlorpheniramine
- Disulfiram
- Erythromycin
- Isoniazid
- Methylphenidate
- Phenothiazine
- Propoxyphene
- Sulthiame
- Tricyclic antidepressants

Effects Decreased by Anticonvulsants:

- Birth control pills
- Cortisol
- Coumarin
- Dexamethasone
- Diazepam
- Digoxin
- Neuroleptics
- Phenylbutazone
- Prednisolone
- Tricyclic antidepressants
- Warfarin

TABLE 10 Carbamazepine Drug Interactions

Decreases Serum Half-Life of:

- Haloperidol
- Phenytoin
- Theophylline

Increases Serum Concentrations of Lithium

Serum Levels Decreased by Simultaneous Administration of:

- Phenobarbital
- Phenytoin
- Primidone

TABLE 11 Valproic Acid Interactions

Decreases Effect of:
Hepatically metabolized drugs
Increases Effect of:
Carbamazepine
Phenytoin

review of this subject the reader is referred to recent papers by Oesterheld and Shader (1998) and Flockhart and Oesterheld (2000).

Although monotherapy should continue to be the preferred choice for children and adolescents with BPD or other severe mood dysregulations treated with anticonvulsants, the combination of two mood stabilizers may become a reasonable option in the treatment of refractory patients. Carbamazepine is a potent stimulator of the hepatic microsomal enzyme oxidation system, while DVP is an inhibitor of this system (Janicak, 1993). If the addition of DPV to CBZ becomes necessary, the clinician should reduce the dose of CBZ, as DVP not only will increase the free fraction of CBZ by displacement of protein binding, but will lead to accumulation of carbamazepine-10,11-epoxide, a metabolite associated with side effects (Rambeck et al., 1990; Ketter et al., 1992).

Parents should be advised to use acetaminophen instead of aspirin when their child develops a fever or cold. The coadministration of aspirin may decrease the clearance of unbound drug and thus require a decrease in the daily dose of DVP (Battino et al., 1995). In addition, cough/cold preparations containing alcohol over 5% may increase the sedative effects of anticonvulsants.

INITIATING AND MAINTAINING TREATMENT

Available preparations and costs of anticonvulsants are shown in Table 12.

There are no current FDA established indications for initiating and maintaining treatment of anticonvulsants as mood stabilizers in child psychiatric disorders. Generally, the guidelines established in treating epilepsy are utilized. Theoretically, children may initially require higher and more frequent doses than adolescents (Battino et al., 1995; Kowatch and Bucci, 1998); nevertheless, in daily clinical practice most child psychiatrists start with low doses and increase the dose carefully monitoring for side effects.

It is important that the child or adolescent undergo a complete history and physical examination prior to the initiation of therapy, as well as a complete blood count with differential and platelet count. Liver function tests, blood urea nitrogen (BUN), and creatinine should be measured. Moreover, patients and fami-

TABLE 12 Available Preparations and Costs of Anticonvulsants

Carbamazepine	
Generic:	
	200 mg scored tablets
	100 mg scored tablets, chewable
Tegretol®:	
	200 mg scored tablets
	100 mg scored tablets, chewable
	100 mg/5 mL oral suspensions
	\$0.90
Valproic acid	
Generic:	
	250 mg capsules
	250 mg/5ml oral syrup
Depakene®:	
	250 mg capsules
	250 mg/5 ml oral syrup
	\$0.84
Divalproex (enteric coated)	
Generic:	
	125, 250, 500 mg unscored tablets
Depakote®:	
	125, 250, 500 mg unscored tablets
	“Sprinkles,” can be put directly on food
	\$1.14
Phenytoin	
Generic:	
	100 mg tablets
	Extended 100 mg capsules
Dilantin®:	
	30, 50, 100 mg scored, chewable tablets
	30 mg/5 mL and 125 mg/5 mg oral suspension
	Extended 30, 50, 100 mg scored, chewable capsules
	Extended 30 mg/5 mL and 125 mg/5 mL oral suspension
	Parenteral formulations
	\$0.10

lies should be educated about possible side effects, as some of them can occur suddenly despite careful monitoring. Adolescent female patients should be informed that anticonvulsants cross the placenta, and that therefore elected or inadvertent pregnancy should be discussed with their physician.

Anticonvulsants have been known to interfere with and alter standard diagnostic laboratory tests. Patients on CBZ may have false negative pregnancy tests if HCG is being assayed (Lindhout and Meinardi, 1982). Also, thyroid function tests (Kleiner et al., 1999) and urinary tests (i.e., false-positive ketones) may be altered.

For clinical follow-ups of patients with mood disorders, we recommend the use of the Life Chart Methodology (LCM) (Denicoff et al., 1997b). It provides a detailed mapping of weekly mood fluctuation, which may help the clinician optimize and rationalize medication therapy (Denicoff et al., 1997).

Carbamazepine

Carbamazepine is supplied in 200 and 100 mg (chewable) tablets and in oral suspension 100 mg/5 mL. Dosage must be carefully and slowly adjusted according to individual response (American Hospital Formulary Service, 1996) and side effects. The initial dosage for the management of seizure disorders in adults and children older than 12 years of age is 200 mg twice daily (as tablets) (Table 13) (American Hospital Formulary Service, 1996). The initial oral dose for the management of seizure disorders in children ages 6–12 years is 100 mg twice daily (or 50 mg 4 times daily as oral suspension). For children under 6 years of age, the starting dose should be even lower, i.e., 50 mg twice daily or 5 mg/kg daily. In children above age 6, dosage may be increased every 5–7 days by 100 mg using a 3- or 4-times-daily divided dosing regimen until the optimum response is obtained (American Hospital Formulary Service, 1996). If the titration is well

TABLE 13 Dosage Schedule for Treating Children and Adolescents with Carbamazepine

Children under 6 years: Use with caution. Start dose of 50 mg b.i.d. (5 mg/kg daily).
Children 6–12 years: Start with 100 mg b.i.d or 50 mg q.i.d. as oral suspension and increase every 5–7 days by 100 mg using t.i.d. or q.i.d. dosing regimen. Maximum dose of 1000 mg/day recommended in children 15 years and younger.
12 years and older: Start with dose of 200 mg b.i.d. Increase by 100 mg every 5–7 days to maximum dose of 1200 mg/day (10–50 mg/kg/day).
Serum levels of 4–12 µg/ml are considered therapeutic for seizure control but undetermined for pediatric mood disorders.

tolerated, the dosage should be increased to a maximum of 1000 mg/day in children younger than 15 years. In children 15 years and older, the dose can be increased to a maximum of 1200 mg/day (American Hospital Formulary Service, 1996). This generally corresponds to a range of 10–50 mg/kg/day. Serum levels of 4–12 µg/mL are considered therapeutic for seizure control (Trimble, 1990a). No equivalency has been determined for the treatment of pediatric mood disorders.

Complete blood count and differential, platelet count, BUN, creatinine, serum iron and liver function tests should be drawn monthly after beginning treatment and then once every 3–6 months (Trimble, 1990a). Monitoring of serum anticonvulsants may be valuable (Hernandez-Fustes et al., 1999) after a recent change in medication dose or when lack of compliance is suspected. White blood cell counts with differential and platelet count and liver function tests are warranted if there is unexplained bruising or bleeding.

Divalproex Sodium

Valproic acid is supplied as divalproex sodium delayed-release 125, 250, 500 mg tablets; divalproex sodium-coated particles in 125 mg capsules (sprinkles), which may be swallowed with soft food; valproic acid 250 mg capsules; valproic acid syrup (250 mg/5 mL), and sodium valproic acid solution for IV infusion (Depacon™) (100 mg/mL). Evidence from studies in adults with BPD suggests that the antimanic activity of DVP becomes most pronounced after achieving serum concentrations of 45 µg/mL or greater (Bowden et al., 1996).

The initial oral dose for treatment of mania in adolescents is 15 mg/kg/day in divided doses (bid) (Table 14). The initial dose can be increased every 3 days by 10 mg/kg/day and titrated upward (or downward) based on clinical response and side effects. The maximum daily dose is 60 mg/kg/day. A plasma level should be obtained 5–7 days after the acute dose is introduced to achieve

TABLE 14 Dosage Schedule for Treating Children and Adolescents with Divalproex Sodium

Not recommended for children less than 3 years of age due to increased liver toxicity.
Use with caution in mentally retarded children due to increased sensitivity to liver failure.
Children >3 years: Dose initiated at 15 mg/kg/day and increased at weekly intervals to a maximum of 60 mg/kg/day.
Target therapeutic levels of 50–125 µg/ml.
Children <10 years: Check liver function tests and complete blood counts monthly for first 2 months and then every 4–6 months.

therapeutic levels in the range of 50–125 µg/mL. Liver enzymes should be measured at baseline, every 3 months during the first semester, and every 6 months thereafter.

Liver function tests should be obtained every month in children less than 10 years of age (Trimble, 1990a). For older children and adolescents, liver function tests and complete blood counts should be drawn monthly for the first 2 months of therapy and then every 4–6 months.

Treatment Duration

There are no established guidelines for duration of treatment with anticonvulsants in children and adolescents with psychiatric disorders. The length of treatment is dependent on a risk/benefit ratio involving side effects versus therapeutic response. Theoretically, anticonvulsants could be given indefinitely to children with BPD who are in remission. Gradual tapering of the medication and switch to a different agent should be considered if side effects are impacting treatment care.

NEW (THIRD-GENERATION) ANTICONVULSANTS

Several new drugs have been recently approved by the U.S. Food and Drug Administration for the control of seizures (Curry and Kulling, 1998). Three of these—gabapentin, lamotrigine, and topiramate—are approved for use in adults with partial seizures. Felbamate had a high incidence of severe side effects (i.e., aplastic anemia and liver failure) and was removed from the market. Its use has been restricted to the treatment of Lennox-Gastaut syndrome (Kohler and Hoffmann, 1998). Lamotrigine and gabapentin are used as add-on therapy in partial seizures in children above 12 years of age (Table 15). There is limited experience with these drugs in children; therefore, none of them is considered a first choice in any epileptic childhood disorder (Kohler and Hoffmann, 1998).

Initial studies suggest that lamotrigine, sodium channel blocker, and glutamate-release inhibitor (Bowden et al., 1999; Suppes et al., 1999), may have a bimodal spectrum of efficacy in the treatment of BPD, especially in mixed phases of BPD (Calabrese et al., 1998) and rapid-cycling bipolar illness (Fatemi et al., 1997). In a recent pilot study, 16 out of 22 (72%) adolescents with BPD treated with additional lamotrigine during their depressed phase responded by the end of week 4, suggesting that lamotrigine might be useful in adolescent bipolar depression (Kusumakar and Yatham, 1997).

Nevertheless, a few cases of Stevens-Johnson syndrome, a potentially lethal condition, associated with the use of lamotrigine have been reported (Messenheimer et al., 1998). The incidence of cases with this syndrome is 0.1% for adult patients and 0.5% for pediatric patients (Messenheimer et al., 1998). Benign rashes commonly associated with lamotrigine (and other anticonvulsants), typi-

TABLE 15 Dosage Schedule for Treating Children and Adolescents with New (Third-Generation) Anticonvulsants^a

Lamotrigine
Children under 16 years: not recommended
Children 16 years and older: careful evaluation of risk/benefits in severe bipolar disorder refractory to all interventions
Gabapentin
Children <12 years of age: not recommended
Children >12 years of age: careful evaluation of risks/benefits in severe bipolar disorder refractory to all interventions
Topiramate
Children <12 years of age: not recommended
Children >12 years of age: careful evaluation of risks/benefits in severe bipolar disorder refractory to all interventions

^a None are considered first-line drugs.

cally occurring within the first 8 weeks of treatment, are difficult to differentiate from Stevens-Johnson syndrome. While the risk for skin rash is higher in the first 8 weeks, the available data are still insufficient to determine when the risk is highest. When a rash develops, we advise discontinuing the medication and seeking medical consultation. The use of lamotrigine in children (especially younger than 16 years of age) with psychiatric illnesses cannot be endorsed at the present time as first-line therapy until additional safety and efficacy data are available. However, with careful evaluation of the risk/benefit ratio, lamotrigine could be considered in adolescents older than 16 years of age with severe (non- acutely manic) bipolar disorder refractory to all interventions.

A few (McElroy et al., 1997; Knoll et al., 1998), but not all (Dimond et al., 1996; Pande et al., 1999), preliminary reports suggest that gabapentin may have antimanic efficacy in adults with BPD. At the time of this publication, only one case of a manic adolescent responsive to gabapentin for the treatment of mania has been reported (Soutullo et al., 1998). Conversely, 12 cases of aggressive behavior associated with gabapentin in children with seizures have been reported (Wolf et al., 1995; Lee et al., 1996; Tallian et al., 1996), making the use of gabapentin in pediatric mood or anxiety disorders empiric and inconclusive. Controlled studies of efficacy and safety are necessary in pediatric samples before gabapentin can be recommended as a mood stabilizer for children with BPD. A careful evaluation of the risk/benefit ratio should precede the consideration of gabapentin in adolescents older than 12 years of age with severe bipolar disorder refractory to all interventions.

Topiramate, reportedly a glutamate-release antagonist and a GABA reuptake inhibitor, has shown antimanic and possibly antidepressant efficacy in treat-

ment-refractory manic patients with BPD type I (Calabrese et al., 1998). Suppes and colleagues (1998) recently evaluated the clinical effectiveness and possible weight loss potential of topiramate in 31 manic/hypomanic patients who completed a minimum of 2 weeks adjunctive topiramate treatment. They reported improvement in 50% of the initially hypomanic/manic and depressed patients at 90 days of treatment at a mean dose of 189 ± 117 mg. Of note, topiramate adjunctive treatment was associated with a mean weight loss from one month to last evaluation of 11 ± 14 pounds. A recent randomized study has shown that topiramate may have cognitive side effects (Martin et al., 1999), i.e., declines on measures of attention and word retrieval difficulties, worrisome potential side effects not systematically studied so far in children and adolescents.

In conclusion, none of these new anticonvulsants has enough efficacy and safety data at the time of this publication to support an off-label first-line therapy indication in pediatric psychopharmacology. Their empiric use, after careful evaluation of individual risk/benefit ratio, remains restricted to adolescents (and occasionally preadolescents) with severe bipolar disorder refractory to all standard interventions. Investigators and clinicians should monitor the evolving pediatric neurology and child psychiatry literature when prescribing these medications to children and adolescents with psychiatric disorders.

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15

Anxiolytics

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Anxiolytic and sedative agents are among the most frequently prescribed drugs in Medicine. However, “anxiolytic” is a deceiving term for this category. Antidepressants are the long-term treatment of choice for most anxiety disorders in adults as well as in children and adolescents, and are discussed separately (see Chapters 8, 9, and 10). Similarly, antipsychotics, which are often used for their sedative and anxiolytic properties, are reviewed in Chapter 12. Beta-adrenergic antagonists have also been used for their putative anxiolytic properties and are reviewed in Chapter 16. Therefore, although the medications discussed in this chapter are commonly known as anxiolytics, they do not necessarily represent current standards of treatment for childhood anxiety disorders. The distinction is an important one, since most anxiolytics are actually of limited use for children and adolescents. Perhaps most disturbing of all is the lack of controlled studies for these agents for treating childhood-onset neuropsychiatric disorders (Riddle et al., 1999).

Thirty-five years ago this category could have been defined as those medications that produce prompt sedation, rapid tolerance, and possible drug dependence. They included the barbiturates, which were widely prescribed as hypnotics and anxiolytics, the newly developed benzodiazepines, which offered improved

efficacy with less risk of toxicity, and the sedating antihistamines. Since barbiturates are now all but absent from the psychiatrist's armamentarium, the term anxiolytic has become nearly synonymous with benzodiazepine. However, antihistamines continue to see frequent use as hypnotics and anxiolytics (in our experience, particularly in the primary care setting) as well as newer categories of novel sedating nonbenzodiazepine hypnotics (zaleplon/sonata and zolpidem tartrate/ambien) and the nonsedating, nonaddictive anxiolytic azapirones. Therefore, this chapter will focus on the current use of benzodiazepines, antihistamines, nonbenzodiazepine hypnotics (zaleplon and zolpidem), and azapirones (buspirone) in child and adolescent psychiatry.

CHEMICAL PROPERTIES

Benzodiazepines

Since their introduction in the early 1960s, benzodiazepines (BZPs) have become the most widely prescribed psychoactive agents in the world, owing to their ease of use, relatively low toxicity, and their potent antianxiety, hypnotic, anticonvulsant, and muscle relaxant effects (Dantzer, 1985). Although specific agents have undergone wide swings in popularity, the overall market for BZPs has remained rich. Over 17 million prescriptions for these agents were filled in 1989 in the United States (Greenblatt, 1991a). The BZPs are so effective at relieving anxiety that they have also become one of the most widely abused prescription drugs, prompting New York State to institute mandatory triplicate prescription regulation for all BZPs (Schwartz & Blank, 1991). However, it is clear that the majority of prescriptions are not abused and BZPs are likely to remain useful for specific conditions (Salzman, 1991).

Absorption and Metabolism

Specific pharmacokinetic data in children and adolescents on BZPs is available only for diazepam (Clein and Riddle, 2001). These agents are more rapidly absorbed and metabolized in children than in adults (Simeon, 1993).

Chlordiazepoxide (Librium) was introduced in 1960 for the treatment of anxiety, followed closely by diazepam (Valium). Many agents are now available and can be classified by chemical structure (Fig. 1) or metabolic pathways (Fig. 2). Kaplan and Sadock (1991) categorize the compounds as 2-keto, 3-hydroxy-, or triazolo-benzodiazepines, corresponding to their structures and metabolic pathways. All are rapidly absorbed via oral or parenteral routes. Only lorazepam has reliable intramuscular absorption. The 2-keto-BZPs (diazepam, chlordiazepoxide) undergo a complex sequence of hepatic biotransformations, the end product of which is the active metabolite desmethyldiazepam. The elimination half-life of this metabolite is approximately 72 hours, and it accounts for the long dura-

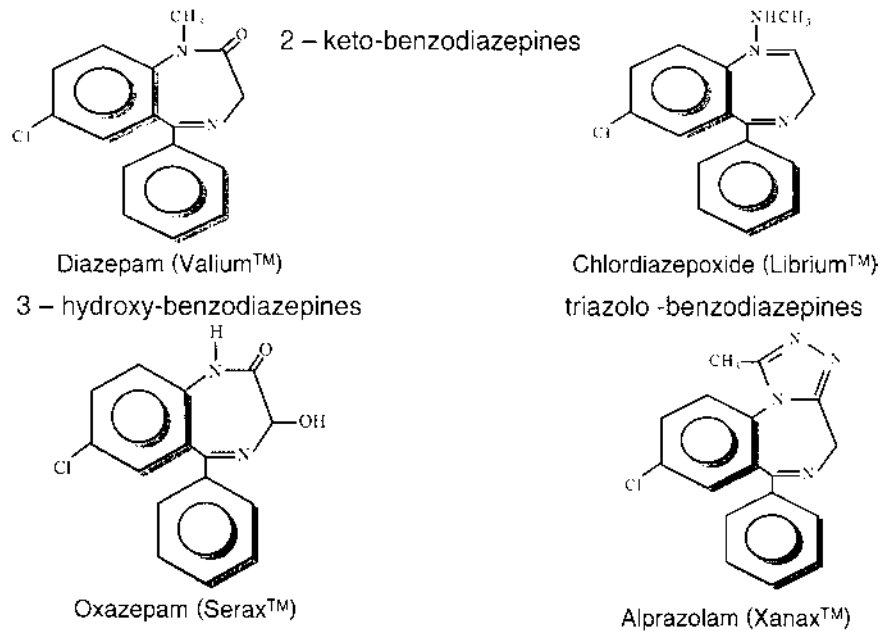


FIGURE 1 Chemical structures of common benzodiazepines.

tion of action seen with 2-keto-BZPs (Table 1). The 3-hydroxy-BZPs (temazepam, oxazepam) are the metabolic products of desmethyldiazepam and do not give rise to further active metabolites. These compounds and their derivatives (lorazepam) are glucuronidated and then excreted, yielding intermediate half-lives of 8–24 hours. Triazolo-BZPs (alprazolam, triazolam) undergo hydroxylation followed by glucuronidation and have intermediate or short half-lives with no active metabolites (Lader, 1983). Although flurazepam is considered a 2-keto-BZP, its metabolic pathway differs. For both flurazepam and quazepam, the rate-limiting active metabolite is desalkylflurazepam, which has a half-life of 48–120 hours (Greenblatt, 1991a). Clonazepam follows a unique metabolic pathway, but its half-life in adults is comparable to those of chlordiazepoxide and diazepam.

Surprisingly, the metabolism of BZPs in newborns has been better characterized and is better understood than in older children. Infants gain the limited ability to metabolize diazepam at around 13 weeks of gestation and reach maximum capacity in early childhood (Coffey, 1990). Thereafter, the general principles of preadolescent pharmacodynamics probably hold true: faster hepatic metabolism necessitates more frequent and higher (weight-corrected) doses for children than for adults. This is supported by studies of midazolam and diazepam,

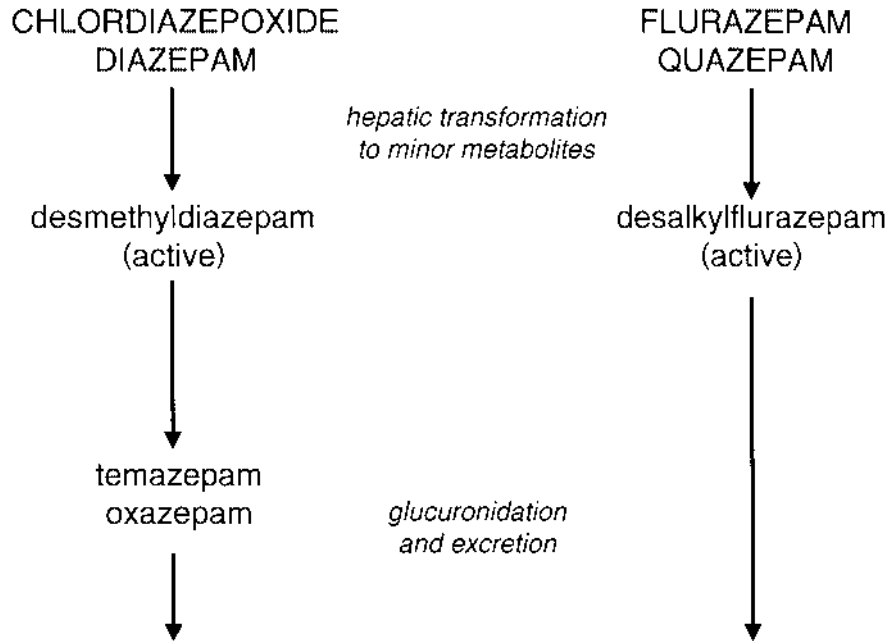


FIGURE 2 Major metabolic pathways of benzodiazepines.

which have half-lives in children of 1.2–2.4 and 18 hours, respectively (Morselli et al., 1973; Payne et al., 1989; Rey et al., 1991). The BZPs that do not undergo hepatic transformation are less affected by increased metabolic rates in children. Metabolic rates in adolescents resemble those in adults (Coffey et al., 1983).

Mechanism of Action

Several hypotheses have been proposed to explain the clinical effects of BZPs. The most prominent followed the discovery that these drugs bind to specific neuroreceptors, for which an endogenous ligand has not yet been found (Lippa et al., 1979; Haefely, 1988). This receptor (BZP-R) apparently mediates the anxiolytic properties of BZPs, since affinity for BZP-R is highly correlated with clinical potency (Mohler and Okada, 1977). The BZP-R function is also closely linked with the gamma-aminobutyric acid (GABA) system and the GABA receptor. The BZP-R agonists increase GABA transmission, while GABA agonists enhance the binding of BZPs to their receptor (Tallman and Gallager, 1979).

Tolerance develops quickly to the sedative and muscle-relaxant properties of BZPs, but less obviously to their anxiolytic properties. Most BZPs maintain anxiolytic efficacy during long-term treatment, but withdrawal does produce

TABLE 1 Sample of Available Benzodiazepines, Usual Adult Doses, and Costs

Compound (Brand name)	How available	Age range	Adult half-life (hr)	Usual adult daily dose	Approximate daily cost ^a
Lorazepam (Ativan)	INJ—2,4 mg/mL Tab—0.5, 1.0, 2.0 mg	>12 years	12	2–6 mg/day divided	\$2.58
Przepam (Centrax)	Tab—5, 10, 20 mg	≥18 years	30–200	20–60 mg/day divided	\$2.81
Chlordiazepoxide (Librium)	INJ—100/2 mL Tab—5, 10, 25 mg Cap—5, 10, 25 mg Tab—15	≥12 years	24–48	5–25 mg b.i.d. or t.i.d.	\$1.55 ^b
Oxazepam (Serax)	Cap—10, 15, 30 mg Tab—3.75, 7.5, 15 mg SR—11.25, 22.5 mg	≥6 years	6–11	10–30 mg t.i.d. to q.i.d.	\$2.08
Clorazepate (Tranxene)	INJ—5/mL Tab—2, 5, 10 mg SR—15 mg	≥9 years	30–200	15–60 mg/day divided	\$4.81 ^b
Diazepam (Valium)	Tab—0.25, 0.5, 1.0, 2.0 mg	≥6 months	20–100	2–10 mg t.i.d. to q.i.d.	\$1.60
Alprazolam (Xanax)	Cap—15, 30 mg INJ—1, 5 mg/mL	≥18 years	6–27	5–6 mg/day divided (for panic disorder) 15 or 30 mg q.h.s.	\$4.33
Temazepam (Restoril)	Cap—15, 30 mg	≥18 years	9–12	No approved psychiatric indication	\$0.84 ^b
Midazolam (Versed)	INJ—1, 5 mg/mL	≥18 years	1–12		NA
Flurazepam (Dalmane)	Cap—15, 30 mg	≥15 years	40–100	15 or 30 mg q.h.s.	\$0.74 ^b
Quazepam (Doral)	Tab—7.5, 15 mg	≥18 years	40–100	7.5 or 15 mg q.h.s.	\$0.88
Triazolam (Halcion)	Tab—0.125, 0.25 mg	≥18 years	2–6	0.25 or 0.125 mg q.h.s.	\$0.89
Estazolam (Prosom)	Tab—1, 2 mg	≥18 years	10–24	1 or 2 mg q.h.s.	\$1.05

^a Cost estimates based on median effective adult dose for primary psychiatric indication and average wholesale price as published in *Prescription Pricing Guide*, Medi-Span, Inc., June 1992.

^b Generic available.

Abbreviations: INJ = injectable; TAB = tablet; CAP = capsule; SR = sustained release.

anxiety symptoms, and this suggests some degree of tolerance (Pollack et al., 1986; Nagy et al., 1989). Although BZP-R does not undergo clear downregulation in response to chronic BZP exposure, there are reports of both downregulation (Miller, 1991) and upregulation (DiStefano et al., 1979). Biochemical studies also suggest multiple subtypes of BZP-R (Lippa et al., 1979; Squires et al., 1979). Some BZPs possess other receptor affinities that account for additional properties such as the antidepressant effect of alprazolam, which is presumed to be related to activity at catecholamine receptors.

Those BZPs marketed exclusively as hypnotics have shorter elimination half-lives and are preferred for their relative freedom from daytime sedation after a bedtime dose. There is evidence that the quality of sleep induced by BZPs differs among specific drugs. For example, alprazolam and diazepam reduce sleep latency and awakenings with equal efficacy, but alprazolam is a more potent REM suppressant (Bonnet et al., 1981). In addition to promoting sleep, BZPs slow reaction time and impair general cognitive abilities (Werry, 1982; Barbee et al., 1992). Therefore, academic function may be affected in children when long-acting agents or daytime doses are used.

Nonbenzodiazepine Hypnotics

No specific pharmacokinetic data is available for zolpidem tartrate (Ambien) or zaleplon (Sonata). Both have enjoyed considerable press and attention for putative superiority of hypnotic effects over the BZPs. In adults, zolpidem has a short half-life of 2.5 hours and has been reported to improve sleep quality and quantity with increased total sleep time (Lahmeyer et al., 1997) and decreased awakenings during the night as compared to placebo (Roth et al., 1995). Moreover, a multicenter, double-blind, placebo-controlled study of zolpidem for the treatment of transient insomnia demonstrated that patients on zolpidem reported feeling more rested and alert the next morning (Biondi and Casadei, 1995). The manufacturer of zolpidem also recommends that patients who take this agent do so if they are planning to get at least 7–8 hours of sleep (Physicians' Desk Reference, 2001). As with hypnotic BZPs, the manufacturer of zolpidem also advocates limiting use of this agent to 7–10 days and not dispensing over 1 month's supply of medication (Physicians' Desk Reference, 2001). Caution is also required when prescribing these agents to patients with a history of substance abuse or dependence, who may be at increased risk for habituation and dependence. Although there are no controlled data in children and adolescents, this agent is being increasingly prescribed in children and adolescents (typically at 5–10 mg doses). However, we believe that further study is indicated before this agent can be indicated for use in children and adolescents.

The recent indication of the non-benzodiazepine hypnotic zaleplon (Sonata) has also generated considerable publicity for its efficacy in treating insomnia by

improving sleep time with a relatively favorable side effect profile (Elie et al., 1999) [Sonata (zaleplon) prescribing information, Wyeth-Ayerst Laboratories, Philadelphia, PA]. It should be noted, however, that zaleplon treatment has not been shown to be superior to placebo in reducing awakenings during sleep or in increasing total sleep duration. Headache, dizziness and sedation were the most common side effects reported [Sonata (zaleplon) prescribing information, Wyeth-Ayerst Laboratories, Philadelphia, PA]. As with the BZPs, the manufacturer, Wyeth-Ayerst, recommends using caution when administering the agent to patients with a history of substance abuse or dependence and prescribing the medication for time-limited periods (e.g., 7–10 days). There are no controlled studies of zaleplon in children and adolescents, and this agent cannot be endorsed for use in the pediatric population at this time.

Buspirone

Buspirone is a novel anxiolytic agent that cannot be classified with other common agents. Buspirone has no approved clinical indications for patients younger than 18 years, and few controlled pediatric studies have been conducted. However, it is marketed for adults as an anxiolytic agent with minimal sedation and abuse potential (Lader, 1991), making it of great potential interest to pediatricians and child psychiatrists. As discussed below (see “Indications”), its benign side effect profile has no doubt contributed to its increasing use for disorders other than anxiety, including depression, attention-deficit hyperactivity disorder (ADHD), and oppositional defiant and conduct disorders (Riddle et al., 1999).

Absorption and Metabolism

Buspirone is the first azapirone anxiolytic to be marketed in the United States, and it is distinct from the BZPs in both structure and function (Fig. 3). It is rapidly absorbed and reaches peak plasma levels in 60–90 minutes in adults. Clinical anxiolytic effects require 2–4 weeks of chronic administration. The mean half-life of the parent compound is 2–3 hours (Gammans et al., 1986), but the primary metabolite [1-(2-pyrimidinyl)-piperazine] is pharmacologically active with a much greater concentration in the brain than its parent compound and a mean half-life of 6.1 hours (Jann, 1988). No pharmacokinetic studies have been conducted in children (Hughes and Preskorn, 1994; Kutcher et al., 1995).

Mechanism of Action

The most prominent pharmacological action of buspirone is agonist binding to postsynaptic serotonin receptors (5-HT_{1A}), and this probably represents the anxiolytic mechanism of action (Temple et al., 1982; Markovitz et al., 1990; Tunnicliff, 1991). 5-HT_{1A} receptors are located in both presynaptic (dorsal raphe nucleus of the midbrain) and postsynaptic regions (hippocampus) (Blier et al.,

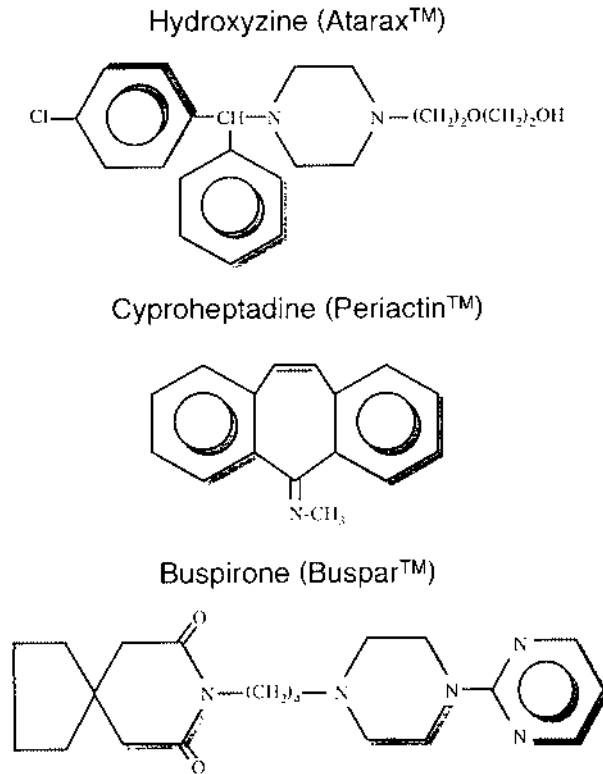


FIGURE 3 Chemical structures of common nonbenzodiazepine anxiolytic drugs.

1990; Andrews & File, 1993). Buspirone and other 5-HT_{1A} agonists exert both presynaptic and postsynaptic actions through desensitization of 5-HT_{1A} receptors on presynaptic neurons, which thereby increases the tonic activation of postsynaptic 5-HT_{1A} receptors. Presynaptically, the 5-HT_{1A} receptor functions as an autoreceptor with negative feedback inhibition, resulting in decreased serotonin neurotransmission and synthesis, while postsynaptic serotonin levels increase (Blier et al., 1990; Andrews and File, 1993). It is possible, therefore, that, depending upon the particular clinical condition and associated neurochemistry, buspirone administration could either increase or reduce serotonin neurotransmission and synthesis (Sussman, 1994).

Buspirone binds to a lesser degree to 5-HT₂ receptors, and this has also been postulated to be involved in its anxiolytic effect (Taylor and Hyslop, 1991).

Buspirone also binds to dopamine (D2) receptors and increases dopamine synthesis and release (Tunnicliff et al., 1992) by inhibiting presynaptic dopaminergic receptors, resulting in inhibition of GABAergic effects on dopamine neurons in the substantia nigra (Eison and Temple, 1986). In addition, buspirone functions as a partial alpha-adrenergic receptor agonist (Castillo et al., 1993) and increases noradrenergic release from the locus ceruleus (Sanghera et al., 1982). The relevance of these affinities to clinical effects is unknown, although Malhotra and Santosh (1998) hypothesized that these affinities suggested possible efficacy for buspirone in the treatment of ADHD.

One of the postulated advantages of buspirone over BZPs is that it does not interact with the BZP-GABA receptor complex, thereby avoiding the addictive properties of BZPs (Tunnicliff, 1991). Accordingly, buspirone possesses no anti-convulsant or muscle-relaxant properties (Jann, 1988), nor does it cause the cognitive impairment seen with BZPs and antihistamines (Barbee et al., 1992; van Laar et al., 1992). Buspirone produces minimal sedation and is, therefore, ineffective as a hypnotic (DiStefano et al., 1979; Manfredi et al., 1991). Antidepressant qualities are hypothesized for buspirone (Robinson et al., 1989; Rickels et al., 1991) but have not been adequately evaluated, particularly in children and adolescents (Eison, 1990).

Other azapirone partial agonists at presynaptic and postsynaptic 5-HT₁ receptors, including gepirone, ipsapirone, tandospirone, and flesinoxan, are not available for use in the United States, although preliminary investigation in adults suggests potential clinical use (Dubovsky, 1990; Mosconi et al., 1993; Rodgers et al., 1994; McGrath et al., 1994; Cutler et al., 1994; Evans et al., 1994).

Antihistamines

Antihistamines have a wide variety of uses in psychiatry and medicine, from the treatment of allergic rhinitis to preanesthetic sedation. Of those used in psychiatry (Table 2), the most common is diphenhydramine (Benadryl). This drug has both antihistaminic and anticholinergic properties and is commonly used as a hypnotic or to treat extrapyramidal symptoms induced by antipsychotic drugs (see Chapter 12). One antihistamine (hydroxyzine) has been approved by the FDA for the short-term treatment of anxiety, although its efficacy has not been well documented. Several others are used for sleep induction or the acute management of agitation.

Absorption and Metabolism

Antihistamines are rapidly absorbed after oral administration and undergo hepatic metabolism. Intramuscular and IV routes are available for diphenhydramine and promethazine but are usually reserved for the treatment of extrapyramidal symp-

TABLE 2 Sample of Available Antihistamine Agents, Usual Adult Doses, and Costs

Agent (Brand name)	Available Forms	Adult half- life (hr)	Dose range	Psychiatric indications	Approximate cost ^a
Diphenhydramine (Benadryl)	CAP—25, 50 mg	3–14	≤5 mg/kg/day, div q.i.d. Max. 300 mg/day	EPS Hypnotic	\$0.37 ^b
	INJ—1, 5, 50 mg/mL				
Hydroxyzine (Atarax, Vistaril)	TAB—10, 25, 50, 100 mg	3–29	50–100 mg as hypnotic 50–100 mg/day, divided	Anxiety Sedation	\$0.89 ^b
	LIQ—2 mg/5 mL				
Cyproheptadine (Periactin)	TAB—4 mg	<5	0.6 mg/kg as sedative 0.25 mg/kg/day, divided	None	NA
	LIQ—2 mg/5 mL				
Promethazine (Phenergan)	TAB—12.5, 25, 50 mg	>5	Max. 16 mg/day 1.1 mg/kg single dose	Hypnotic Sedation	\$0.31 ^b
	SUP—12.5, 25, 50 mg				
	LIQ—6.25, 25 mg/5 mL INJ—25, 50 mg/mL				

* Cost estimates based on median effective adult dose for primary psychiatric indication and average wholesale price as published in *Prescription Pricing Guide*, Medi-Span, Inc., June 1992.

^b Generic available.

Abbreviations: CAP = capsule; TAB = tablet; INJ = injectable; LIQ = liquid; SUP = suppository.

toms or severe allergic reactions or for immediate sedation. Sedative effects reach their peak 1–3 hours after an oral dose and average 4–6 hours in duration (Physicians' Desk Reference, 2001). All antihistamines used for psychiatric indications have short elimination half-lives (Table 2). The manufacturers report half-lives of less than 5 hours for all commonly used agents. However, in practice, the half-life of diphenhydramine varies from 3 to 13 hours (Simons et al., 1990). Estimates for hydroxyzine likewise vary from 3 to 29 hours (Simons et al., 1989). As with the BZPs, children metabolize antihistamines more rapidly than do adults. The half-life of diphenhydramine in children is 40% of that in elderly adults and 60% that in young adults (Simons et al., 1990). Children metabolize hydroxyzine approximately three times faster than do adults (Simons et al., 1989).

Mechanism of Action

The antihistamines used in psychiatry produce sedation through central histamine H₁ receptor blockade, but their chemical structures are diverse (Fig. 3). Several newer antihistamines were specifically designed *not* to produce sedation, and they accomplish this by reducing central nervous system (CNS) penetration. No anxiolytic mechanism has been postulated for antihistamines apart from that of general sedation, making these agents of limited use in the long-term treatment of anxiety disorders.

Other properties pertinent to psychiatry are based on nonhistaminic mechanisms. Antiparkinsonian effects are strongly related to anticholinergic properties, making diphenhydramine the most effective agent for this application (see Chapter 17). Cyproheptadine has antiserotonergic properties and has been used in adults to treat sexual dysfunction induced by selective serotonin-reuptake inhibitor (SSRIs) SSRIs (e.g., fluoxetine) and restrictive eating behavior in anorexia nervosa (Kaplan and Sadock, 1991). One sedating antihistamine, promethazine, is a phenothiazine derivative. Although it is a weak dopamine antagonist (one tenth the potency of chlorpromazine), it can produce the side effects common to other antipsychotic drugs (see Chapter 12).

INDICATIONS

Despite the approval of some BZPs for pediatric use, controlled studies of their efficacy in children and adolescents are scarce. Waters (1990) has suggested that their clinical use far exceeds that supported by research. In one large Canadian study, BZP prescriptions were more common than all other pediatric psychotropics combined (Quinn, 1986). Likewise, antihistamines have long been used as sedatives and hypnotics despite a lack of evidence to prove their effectiveness for specific indications. Buspirone is relatively understudied but has several promising applications in child and adolescent psychiatry.

ANXIETY DISORDERS

A recent review has judged anxiety disorders to have the highest point prevalence of any category of child and adolescent psychiatric illness. Between 9 and 17% of children meet criteria for at least one anxiety disorder (Bernstein and Borchardt, 1991). These include syndromes that are diagnosed in adults and children/adolescents (panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, social phobia) and those that are exclusive to children (separation anxiety disorder). Despite the high prevalence of anxiety, the majority of pharmacological trials in children are single case reports or small open trials. This may be partly attributed to the success of nonpharmacological therapies, high placebo response rates for anxiety disorders, inadequate dosing, and short duration (Riddle et al., 1999). For example, specific or simple phobias have never been subjected to systematic pharmacological trials in children but have been shown to respond well to a variety of behavioral and psychotherapeutic and behavioral interventions (Bernstein and Borchardt, 1991). However, many anxiety disorders are not as amenable to psychotherapy, and the lack of complementary pharmacologic trials represents a serious deficit in child and adolescent research.

Panic Disorder

Though panic attacks were at one time considered an adult problem, they most certainly occur in children. A recent Australian survey found that 43% of adolescents reported at least one episode during their lives (King et al., 1993). While panic disorder is very uncommon before puberty (Black and Robbins, 1990; Klein et al., 1992), retrospective investigation of adults with panic disorder suggests that panic disorder frequently has its onset in adolescence and young adulthood (Moreau and Follett, 1993). Von Korff et al. (1985) reported that the peak age of onset of panic disorders was 15–19 years of age. Hayward et al. (1992) found 5.3% of 754 sixth- and seventh-grade pubertal girls in the United States had suffered at least one panic attack. Sexual maturation was strongly associated with panic attacks. Panic attack rates of 8% were observed in females who were sexually mature (Tanner Stage 5) but 0% of sexually immature girls (Tanner Stages 1 or 2). Bernstein et al. (1996) noted that the increased rate of panic attacks associated with increased Tanner Stage was not due to differences in chronological age and suggested that sexual steroid hormones could play an important role in panic attacks.

Estimates of the number of children experiencing at least one moderate to severe panic attack vary from 0.6% to 13.3%, but the rate of panic disorder in children and adolescents has not been fully established (Payne et al., 1989). More than 50% of 194 adult patients with panic disorder were reported to have had childhood anxiety disorders (Pollack et al., 1996). Moreover, adult panic disorder

patients with a history of anxiety disorder in childhood had significantly increased rates of comorbid mood disorders. More than 60% of adult patients suffering from panic disorder had two or more anxiety disorders during childhood. The comorbidity among anxiety and mood disorders must be considered in treatment intervention as well as in the design of controlled investigations to study efficacy and safety of medications for treating anxiety disorders.

The short-term efficacy of BZPs in adult panic disorder is well documented (Aden and Thein, 1980; Maletzky, 1980; Spier et al., 1986; Cohn and Wilcox, 1986; Andersch et al., 1991; Schatzberg, 1991), and alprazolam has received FDA approval for the treatment of panic disorder in patients 18 years of age and older. Experience with BZPs in childhood panic disorder includes case reports of success with clonazepam (Biederman, 1987; Kutcher and MacKenzie, 1988) and the combination of alprazolam with imipramine (Ballenger et al., 1989). Kutcher and Reiter (Riddle et al., 1999) conducted a double-blind, placebo-controlled study of clonazepam in adolescents with panic disorder and found clonazepam to be superior to placebo in reducing symptoms of general anxiety, number of panic attacks, and dysfunction in school and the social setting. Therefore, although it seems likely that the short-term efficacy of BZPs in youngsters will prove similar to that in adults, the long-term efficacy and adverse effects have not been established.

Antidepressants, particularly the SSRIs, are currently the pharmacological treatment of choice for panic disorder in children and adolescents (See Chapter 9), but the conservative use of alprazolam or clonazepam is a reasonable extension of their use in adults (Ballenger et al., 1989). Since the anxiolytic response to BZPs is rapid and response to antidepressants (e.g., SSRIs) may be delayed, this combination provides prompt treatment with a minimal risk of dependence or withdrawal from the BZP. In adults, BZP augmentation of antidepressant treatment may hasten both antidepressant and anxiolytic responses. Therefore, this combination is not uncommonly used in children and adolescents despite the lack of controlled studies.

This approach is not without problems. Woods and colleagues (1992) compared imipramine with combined imipramine and alprazolam in adults and found that although the combined treatment produced a more rapid response, it was also associated with intolerance of the alprazolam taper. The study used alprazolam for up to 6 weeks before attempting a taper, suggesting that if combined treatment is used it should be limited to the first few weeks of therapy. Caution is also indicated in a child or adolescent with a history of substance abuse or dependence or a strong family history of substance abuse or dependence.

Buspirone has been tested for adult panic disorder, but the results do not support its efficacy. Controlled trials have reported failed (Sheehan et al., 1990) or modestly successful (Pohl et al., 1989) treatment of panic attacks. One case series suggested that it may be an effective adjunct to BZP treatment (Gastfriend

and Rosenbaum, 1989), but this requires replication. Unless further controlled trials support its use, buspirone cannot be recommended for child and adolescent panic disorder.

Other 5-HT_{1a} azapirone partial agonists not currently available for use in the United States may, however, merit consideration for treatment of panic disorder. In an open-label study, Pecknold et al. (1993) found gepirone to be effective in treating adults with panic disorder. Further controlled trials of these other 5-HT_{1a} partial agonists are necessary before they can be recommended for child and adolescent panic disorder.

Antihistamines have no application in children and adolescent panic disorder.

Separation Anxiety Disorder/School Refusal

Separation anxiety and the symptoms of school refusal are closely related, since they often coexist and they overlap with the older term "school phobia." Separation anxiety accounts for up to half of anxiety-related treatment referrals in children and adolescents and has a lifetime prevalence of up to 84% in children diagnosed with any anxiety disorder (Last et al., 1992). Up to 80% of children with school refusal meet criteria for separation anxiety disorder (Bernstein and Borchardt, 1991).

Accordingly, the treatment of separation anxiety disorder has been somewhat better studied than other childhood anxiety disorders, and several studies report success with BZPs. In 1962 D'Amato (1962) conducted an open trial of chlordiazepoxide on nine children with school phobia, eight of whom showed excellent results. A few years later, Kraft and colleagues (1965) conducted an open trial of chlordiazepoxide with 130 diagnostically heterogeneous children ranging in age from 2 to 17 years. Of the 18 children with school phobia, 10 were considered "excellent" responders and 4 were considered "good" responders (78%). Two children (11%) became worse. In contrast, 38% of children with a primary behavioral disorder responded and 22% became worse. More recently, a double-blind controlled study of alprazolam. In a study of 18 children and adolescents with separation anxiety disorder treated with clonazepam (0.5–0.6 mg/day), 64% were considered improved by their teachers, 65% by self-reports, 82% by the children's parents, and 89% by their psychiatrists (Kutcher et al., 1992). A double-blind placebo-controlled 8-week study of alprazolam by Bernstein et al. (1990) found a trend toward improvement but no statistically significant benefit in 24 children and adolescents with school refusal. Mean doses of 1.6 mg of alprazolam per day (range 0.5–3.5 mg/day) were used in this study. These children also had no significant improvement on imipramine. More recently, Graae et al. (1994) conducted a double-blind, placebo-controlled crossover study of clonazepam in 15 children with anxiety disorders, primarily separation anxiety disorder. Patients were treated with four weeks of clonazepam

(0.5–2 mg/day) and 4 weeks of placebo. There was no significant difference observed between clonazepam and placebo treatment.

These data are inconclusive. The open trials showing a good response to BZPs were conducted using diagnostic criteria that differ from the current definition of separation anxiety disorder and probably represented a mixed sample of children with school refusal and anxiety. The controlled study by Bernstein et al. (1991) may have been less sensitive to a positive effect because the sample was selected for school refusal rather than for separation anxiety and included children with depressive disorders. Further controlled trials are necessary before the short-term efficacy of BZPs can be established for separation anxiety disorder. The long-term efficacy is unknown.

There have been, as yet, no controlled trials of buspirone for the treatment of separation anxiety disorder, although a case study reported success in a young boy (Kranzler, 1988). Balon (1994) also reported buspirone to be effective in the treatment of an adolescent boy with separation anxiety disorder. Buspirone would seem a viable treatment for this disorder and should be tested in clinical trials.

As with most anxiety disorders, antihistamines have no proved or postulated role in the treatment of separation anxiety disorder.

Generalized Anxiety Disorder (Previously “Overanxious Disorder”)

In recent years there has been increased recognition that generalized anxiety disorder (GAD) is a severe, highly prevalent, and often chronically disabling illness. Its lifetime prevalence was found to be 3.7% in epidemiological catchments area studies of 5596 nonreferred adolescents 14–17 years of age (Whitaker et al., 1990), 2.4% in 1869 12- to 16-year-old children (Bowen et al., 1990), and nearly 3% for 792 children 11 years of age (Anderson et al., 1987). In a sample of 300 children 7–11 years of age studied in the pediatric primary care setting, the prevalence of anxiety disorders was over 15% with the most common conditions being simple phobia, separation anxiety disorder, and GAD (Benjamin et al., 1990). Keller et al. (1992) reported that the median age of onset of GAD was 10 years of age.

Simeon and Ferguson (1987) conducted a single-blind trial of alprazolam in 12 children with overanxious disorder, yielding at least moderate improvement in seven. Simeon et al. (1992) conducted a 4-week, double-blind, placebo-controlled study of alprazolam in 30 children and adolescents with avoidant disorder or overanxious disorder. Mean alprazolam doses were 1.6 mg/day (range 0.5–3.5 mg/day), and 88% of patients completing the study on alprazolam exhibited clinical improvement as compared to 62% of patients treated with placebo, although these differences were not statistically significant. Virtually all other trials of BZPs in general childhood anxiety are diagnostically nonspecific (Table 3).

TABLE 3 Trial of Benzodiazepines for Nonspecific Childhood Anxiety Symptoms

Ref.	Design	No. of subjects	Symptoms	Treatment	Outcome
Gleser et al., 1965	P-C	46	Severe behavioral disorders	Chlordiazepoxide	Improved anxiety and hostility
Kraft et al., 1965	Open	130	Behavior disorders (50) School phobia (18) Adjustment reaction (17) Other (45)	Chlordiazepoxide	Best response—school phobia Worst response—brain damage 13 developed disinhibition No benefit
Lucas and Pasley, 1969	P-C	10	“Psychoneurotic” with anxiety	Diazepam	Slight exacerbation of anxiety compared with placebo
Aman and Werry, 1982	P-C	15	General anxiety and developmental reading delay	Diazepam	Improved depressions and anxiety; worsened impulsivity and psychosis
Petti et al., 1982	Open	9	“Severely disturbed”	Chlordiazepoxide	Improved anxiety before procedures
Pfefferbaum et al., 1987a	Open	13	Anticipatory anxiety prior to bone marrow or spinal tap	Alprazolam	Improved with follow-up of 5–36 months
Biederman, 1987	Open	3	Paniclike symptoms	Clonazepam	Significant improvement in anxiety
Simeon and Ferguson, 1987	P-C	12	Overanxious or avoidant disorder	Alprazolam	Improved anxiety
Hennes et al., 1990	P-C	55	Anticipatory anxiety for laceration repair	Oral midazolam (no longer available in oral form)	Improved anxiety

P-C = Placebo-controlled.

Buspirone has been found to be effective for GAD in adults in double-blind comparisons with diazepam, oxazepam, alprazolam, and lorazepam (Feighner et al., 1982; Newton et al., 1982; Cohn and Wilcox, 1986; Ansseau et al., 1990; Enkelmann, 1991). Other azapirone partial 5-HT_{1a} agonists not currently available in the United States such as ipsapirone (Cutler et al., 1994) appear to be effective in treating GAD. There are no controlled studies in children and adolescents. Buspirone is being increasingly used for children with GAD (Kutcher et al., 1992; Coffey, 1993; Popper, 1993; Maletic et al., 1994). Simeon (1993) conducted an open trial of buspirone (18.6 mg/day, mean maximum dose) for 4 weeks in 15 patients 6–14 years of age with various anxiety disorders and noted significant reductions in anxiety, hyperactivity, and behavior problems with minimal side effects. Adult GAD is currently the only FDA-approved indication for buspirone, but it seems a likely candidate for the future treatment of childhood GAD.

Hydroxyzine, diphenhydramine, and promethazine have been used for non-specific anxiety symptoms in both children and adults but have not been systematically studied. One early controlled study measured decreased physiological and psychological signs of anxiety in a mixed group of adult psychiatric patients after a single intramuscular dose of hydroxyzine (Pishkin et al., 1967), but no data are available on children and adolescents. Although anxiety is an approved indication for hydroxyzine, there is no evidence supporting the long-term benefit of antihistamines in the treatment of anxiety disorders. They are often used and may be effective for anticipatory or situational anxiety, such as a child might experience prior to an office procedure, but this, too, is understudied.

Posttraumatic Stress Disorder

Most research on posttraumatic stress disorder (PTSD) has been conducted on adult war veterans. However, this disorder may also affect children exposed to single or repeated traumatic events, such as sexual abuse, kidnapping, or a natural disaster (Terr, 1983, 1996; McLeer et al., 1988; Golbin and Sheldon, 1992). Antidepressants are the pharmacological treatment of choice for adults with PTSD (see Chapters 8, 9, and 10), but BZPs and buspirone have also been evaluated, with mixed results.

The scant data on BZPs are not favorable. Clonazepam fails to inhibit the hyperactive startle reflex in adults with PTSD (Shalev and Rogel-Fuchs, 1990), and a double-blind, placebo-controlled study of alprazolam in 16 adults found no benefit (Braun et al., 1990). Six patients (three of whom were receiving alprazolam) dropped out of the study because of the drug's ineffectiveness, and those who completed the trial showed a trend toward improvement of anxiety symptoms but no effect on the major symptoms of PTSD. Furthermore, withdrawal effects exacerbated anxiety in subjects receiving alprazolam (Braun et al., 1990). Similar problems with withdrawal were observed in eight combat veterans who

had experienced long-term alprazolam treatment, including severe sleep and anxiety problems, as well as an increase in the major symptoms of PTSD (Risse et al., 1990). The only favorable report is a letter by Feldman (1987), who saw improvement in 16 of 20 war veterans on alprazolam but increased aggressive outbursts in the remaining 4. Based on this limited experience, BZPs cannot be recommended for use in children with PTSD. In fact, these studies suggest that they should be avoided.

In contrast, a single open trial of buspirone in three PTSD patients reported improvement in anxiety, insomnia, depression, and flashbacks on 35–60 mg/day (Wells et al., 1991). Controlled trials of buspirone for PTSD are warranted but have not been conducted, and there are no controlled trials of any agent for childhood and adolescent PTSD.

No studies of antihistamines in the treatment of PTSD have been conducted, nor are they warranted.

Obsessive-Compulsive Disorder

General clinical opinion does not favor the use of BZPs as a primary treatment for obsessive-compulsive disorder (OCD) (Griest, 1990). However, they are not uncommonly used as adjuncts to antidepressants. Much recent research has focused on the antiobsessive properties of the SSRIs and the tricyclic antidepressant clomipramine (see Chapters 9 and 8). Animal studies have demonstrated that clonazepam, in particular, has an indirect effect on serotonergic transmission that is not mediated by reuptake inhibition or receptor binding (Hewlett et al., 1990). This effect provides a theoretical basis for clinical trials of clonazepam in OCD. In an open trial, good symptomatic improvement was observed in three adults with OCD, and it persisted up to one year in two subjects (Hewlett et al., 1990). However, one subject was terminated because she began using alcohol in conjunction with the medication. Benzodiazepines such as clonazepam are frequently used as adjuncts in OCD, particularly when there are high levels of associated anxiety, but recent study suggests that they have little effect on core OCD symptoms (Dominguez and Mestre, 1998). No controlled trials are available, and there is no evidence supporting the use of BZPs in childhood OCD. If they are used to treat severe concomitant anxiety, caution is indicated, particularly in patients with history of substance abuse or dependence or strong family histories of abuse or dependence.

Since buspirone is an agonist at postsynaptic serotonergic receptors, one might predict that it would be useful in treating OCD. Although one open trial did not support the efficacy of buspirone as a single agent (Jenike and Baer, 1988), a more recent double-blind, controlled trial in adults found that 60 mg of buspirone daily was as effective as clomipramine (Pato et al., 1991). Open-label studies have suggested some success in using buspirone in combination with other serotonergic agents, including a case report of buspirone augmenting the

response of fluoxetine in an 11-year-old girl with OCD and depression (Alessi and Bos, 1991). Markowitz and associates (1990) found the combination of buspirone and fluoxetine to be superior to fluoxetine alone in an open trial for young adults with treatment-resistant OCD. In contrast, placebo-controlled studies of SRI augmentation (clomipramine and fluoxetine) with buspirone (Pigott et al., 1992; Grady et al., 1993) have not demonstrated benefit of buspirone vs. placebo augmentation. No studies of buspirone in pediatric OCD are available.

Social Anxiety Disorder (Social Phobia)

Because of their sedative effects, BZPs are typically not recommended for use for social phobia (e.g., performance anxiety). There have been no controlled studies of these agents in children and adolescents. Zwier and Rao (1994) reported benefit of buspirone in an adolescent with social phobia. Further controlled studies of this buspirone are warranted before it can be recommended for the treatment of this condition.

Anticipatory Anxiety Associated with Medical Procedures

The most practical application that may be gleaned from studies of BZPs for anxiety may be in the pretreatment of anticipatory anxiety prior to a painful procedure, as reported by Pfefferbaum and colleagues (1987a). They found that open-label alprazolam treatment (0.125–1 mg/day) was effective in reducing anticipatory anxiety associated with bone marrow aspirations and lumbar punctures in 13 children with cancer. Single doses of BZPs are likely to reduce the psychological trauma of such procedures and are unlikely to produce untoward effects. Hennes et al. (1990) conducted a double-blind, placebo-controlled study of the high-potency, short-acting benzodiazepine midazolam (Versed) (0.2 mg/kg, orally administered) in preschool-age children having surgical repair for lacerations. Midazolam was significantly more effective than placebo in reducing anxiety (70% or 21 of 30 patients treated with midazolam improved as compared to only 12% or 3 of 25 patients treated with placebo). The medication was well tolerated with no adverse events reported. It should be noted that there is no currently available oral preparation of midazolam (Riddle et al., 1999). It is only available to be administered by parenteral injection.

BZP administration for anticipatory anxiety should probably be reserved for developmentally normal children, since two studies have noted that a minority of children exhibit behavioral disinhibition when treated with BZPs and that this effect appears more frequently in children with mental retardation or “brain damage” (Aman and Werry, 1982; Petti et al., 1982). If it is deemed necessary to use these agents in such populations, lower dosing and close monitoring is indicated. Behavioral disinhibition is the most significant risk of using these agents for anticipatory anxiety or as needed (p.r.n.) sedatives (see “Adverse Reactions”).

Buspirone is not likely to be useful for anticipatory anxiety associated with medical procedures since its effect is often delayed.

Conclusions

Controlled pharmacological studies in child and adolescent anxiety disorders are very scarce, so that recommendations for treatment must be drawn from open trials and the adult literature. When pharmacological treatment is necessary, antidepressants are the first-line treatment for panic disorder, separation anxiety disorder, GAD, PTSD, and OCD (see Chapters 8 and 9). BZPs may be useful for the treatment of anticipatory anxiety and for the first 2 weeks of panic disorder therapy in children and adolescents, but they are of questionable benefit in separation anxiety disorder. There is little support for their use for OCD or the long-term treatment of GAD. They should be avoided in the treatment of PTSD based on the lack of demonstrable benefit in adult studies and the possible exacerbation of symptoms upon withdrawal. Many questions remain about optimal agents, dosage schedules, and duration of treatment for any child or adolescent anxiety disorder. Controlled trials of BZPs are most clearly needed for the treatment of separation anxiety disorder and panic disorder, where their efficacy and the risks of long-term therapy in children must be established.

Buspirone has been most promising as a nonaddictive alternative to BZPs for the long-term treatment of GAD in adults. There is almost no research experience with children, but the low risk of dependence and its favorable side-effect profile make this agent more attractive than BZPs for early clinical use. While there are no established indications, possible uses include GAD, OCD, and PTSD. There are no studies of buspirone for separation anxiety disorder, although this would seem a likely application. Buspirone may be less effective than standard agents for panic disorder, but this requires further study in both adults and children.

Finally, hydroxyzine has gained FDA approval for the treatment of anxiety, despite a lack of academic support for this indication. Sedating antihistamines are commonly used for anticipatory and situational anxiety in children and may be appropriate for these indications but are by no means proven. Antihistamines cannot be recommended as the primary treatment for any chronic child or adolescent anxiety disorder.

Insomnia

Insomnia is estimated to afflict 30–35% of the population each year (Mellinger et al., 1985) and is the most common problem for which sedatives and anxiolytics are prescribed. Academic debate concerning the most appropriate use of anxiolytic drugs for insomnia by no means has been concluded, but it seems clear that only a fraction of the prescriptions written for hypnotic drugs are justified. As

used here, the term “hypnotic” will refer to those sedatives and anxiolytics that are commonly prescribed for sleep induction, including primarily antihistamines, short-acting BZPs, and newer non-BZP sleep agents such as zolpidem tartrate (Ambien) and zaleplon (Sonata).

Insomnia is most often secondary to a treatable problem such as concurrent affective illness, pain, or substance use (including caffeine, alcohol, nicotine, and illicit drugs), and in such cases should be addressed through treatment of the primary disorder. Secondary insomnia is not a usual indication for hypnotic drugs. Primary insomnia (also called psychophysiological insomnia) is an approved indication for hypnotic drugs, but since tolerance develops to the sedative properties of BZPs, the non-BZP sleep agents, and antihistamines, they are only effective for a limited time (Hishikawa, 1991). Chronic primary insomnia is not an indication for long-term hypnotic drugs (Vogel, 1992). Therefore, hypnotics are most appropriate for *transient primary insomnia*, loosely defined as cases that last fewer than 30 days. Transient primary insomnia accounts for 15% of cases in adults (Coleman et al., 1982) and is at least as common in children (Dahl, 1992).

Transient insomnia usually follows an acute stressor such as psychosocial problems or circadian phase shifts (Hishikawa, 1991). If sleep does not normalize within 1–2 weeks, then a diagnosis of chronic insomnia or concurrent affective disorder should be considered. Because the disorder is self-limited, pharmacological treatment is often unnecessary and behavioral techniques (structured sleep schedules, improved sleep hygiene), and supportive measures are usually effective (Bootzin and Perlis, 1992; Gillin, 1992). In young children, learning to self-initiate and maintain sleep may represent a developmental and behavioral milestone, making nonpharmacological techniques the clear treatment of choice (Durand and Mindell, 1990; France & Hudson, 1990; Dahl, 1992). Despite the success of nonpharmacological treatments, hypnotic agents are occasionally indicated and are quite often prescribed.

Benzodiazepines

At their introduction to the medical community, BZPs represented a welcome departure from barbiturates, which had been the primary hypnotic agents of the past. As indicated in Table 4, most short-acting BZPs are approved for the short-term treatment of adult insomnia when nonpharmacological measures are ineffective. Virtually all BZP hypnotics reduce sleep latency, arousals, and partial arousals under laboratory conditions. Placebo-controlled trials of up to 5 days' treatment have demonstrated this for specific agents, including alprazolam (Bonnet et al., 1981), quazepam (Tietz et al., 1981; Uhthoff et al., 1981), triazolam (Roth et al., 1974; Rickels et al., 1975), temazepam (Roehrs et al., 1990), and others. The study by Uhthoff and associates (1981) illustrates the effect. Subjects treated with quazepam showed a significant improvement in sleep quality and latency

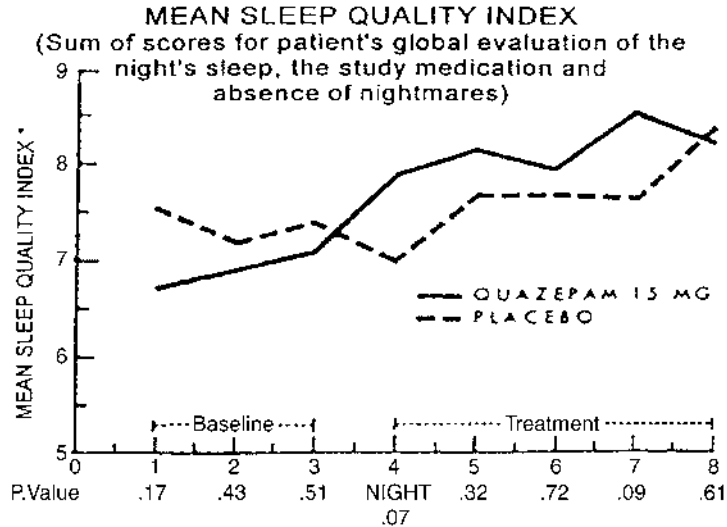
TABLE 4 Approved Indications for Benzodiazepine Drugs

Compound	Anxiety disorder	Insomnia	Procedural sedation	Alcohol withdrawal	Other
Lorazepam	Yes	No	Yes	No	
Prazepam	Yes	No	No	No	
Chlordiazepoxide	Yes	No	No	Yes	
Oxazepam	Yes	No	No	Yes	
Chlorazepate	Yes	No	No	Yes	
Diazepam	Yes	No	Yes	Yes	Muscle spasm
Alprazolam	Yes	No	No	No	Panic disorder
Temazepam	No	Yes	No	No	
Midazolam	No	No	Yes	No	
Flurazepam	No	Yes	No	No	
Quazepam	No	Yes	No	No	
Triazolam	No	Yes	No	No	
Estazolam	No	Yes	No	No	

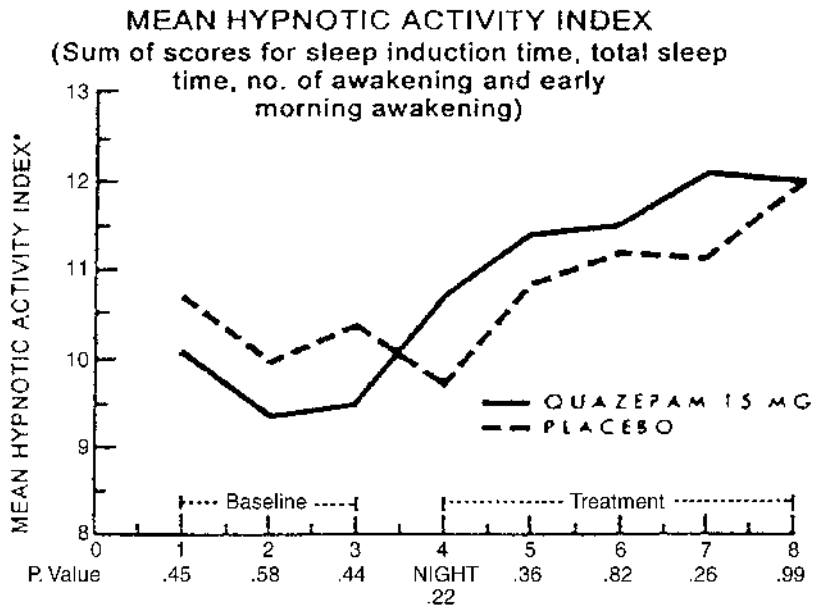
during the first 4 days of treatment but were similar to controls by the fifth day (Fig. 4).

Beyond 5 days of treatment, the effectiveness of BZPs is less certain. Rebound insomnia occurs even after very limited use of hypnotics and may predispose to drug dependence (Kales et al., 1991). Roehrs and colleagues (1992a) found that significant rebound insomnia occurred in both insomniac subjects and noninsomniac controls after six nightly doses of triazolam 0.5 mg. The degree of rebound was similar for patients and controls, but was more severe after abrupt discontinuation. When rebound takes place, the probability that a patient will continue self-administering hypnotics increases with the severity of the initial sleep problem, regardless of whether the subject received active drug or placebo (Roehrs et al., 1992b). This would suggest that *rebound and dependence are of significant concern in insomniac patients treated with BZPs*, although the propensity to self-medicate may be a characteristic of the sleep disorder, as well as of the reinforcing properties of the medication. In addition to these concerns, a reduction in next-day performance and alertness may be experienced after a bedtime dose of a BZP, especially with long-acting agents (see "Adverse Reactions"). Therefore, BZP hypnotics should be used only if the immediate benefits of improved sleep outweighs both the immediate risk of residual daytime effects and the eventual risk of rebound insomnia or drug dependence.

When a patient experiences chronic primary insomnia, short courses of BZPs may be helpful while nonpharmacological measures are being instituted, although the risk of dependence may be greater than with situational insomnia.



* A higher score indicating better sleep (possible score 3.11)



A higher score indicating better sleep (possible score 4.17)

FIGURE 4 Sleep response to quazepam.

Hishikawa (1991) reviewed the use of BZP hypnotics for adult insomnia and recommended that hypnotics be added only in severe cases and that treatment not exceed 3 weeks. The American Psychiatric Association has concluded that there is little evidence supporting the effectiveness of BZP hypnotics past 30 days of treatment (Salzman, 1991).

The aforementioned data are exclusively based on experience with adults. Benzodiazepines, hypnotics have not been well studied in children. They are, however, widely prescribed despite the apparent clinical consensus that BZPs are inferior to behavioral measures and low-dose antidepressants (Quinn, 1986; Richman, 1986; Dahl, 1992). The extant literature does not clearly answer the question of when to use BZP hypnotics, but suggests that they will be most helpful for severe transient insomnia that is related to time-limited stressors. Appropriate situations for children and adolescents might include insomnia following psychosocial or physical trauma, travel to a different time zone, or changing from one work shift to another. Since even single doses may produce rebound insomnia and this effect is worse with abrupt discontinuation, the most appropriate strategy may be to provide two to three therapeutic doses of a short-acting hypnotic followed by tapering the doses over several days. Admittedly, this appears to be the least common prescribing practice. A chart review found that 88% of hypnotic prescriptions written by outpatient primary physicians not only failed to diagnose the type of sleep disturbance, but failed to document sleep symptoms at all. Furthermore, 30% of prescriptions were for 180 or more doses (Shorr and Bauwens, 1992). This is clearly unacceptable for children and adolescents, since chronic BZP prescription may encourage dependence, create iatrogenic sleep and anxiety symptoms, and affect school performance.

Case History

A 14-year-old girl hospitalized for an appendectomy was observed to have insomnia and anxiety. The child psychiatry service was called in to evaluate the patient. The patient had no prior psychiatric history. She denied neurovegetative symptoms of depression and was not suicidal. She had no history of anxiety, insomnia, panic attacks, or the like. According to her parents, she had always been a confident, rather calm child. This was, however, her first hospitalization, and she admitted to being scared even though her mother or father was with her throughout the day and night. She had no history of drug or alcohol use or abuse. The family history was negative for anxiety disorders, panic disorder, phobia, and psychiatric disorders, such as depression or bipolar disorder. Significantly, there was no history of substance abuse disorders in the family. A trial of relaxation training exercises, including having the patient listen to relaxing tapes and being instructed in breathing techniques to relieve anxiety, was initiated. This was quite effective in reducing the child's anxiety, but not effective in ameliorating her sleep disturbance. In view of the patient's continued insomnia, and since she had

no personal or family history of substance-abuse disorders, a short-term trial of triazolam 0.125 mg q.H.S. for insomnia was initiated. The patient tolerated this dose well the first night it was prescribed and slept 8 hours of uninterrupted sleep. The next two nights, she again requested triazolam 0.125 mg. Each night her insomnia was relieved. By her third and final night in the hospital, she was feeling much happier and looking forward to returning home. The operation had been successful and she was observed joking with the nursing staff. She did not request triazolam for insomnia on this night. She subsequently slept soundly for the entire night and was discharged home. Subsequent follow-up revealed that she was doing quite well medically and psychologically. She showed no evidence of anxiety or insomnia and was not requesting medication to calm her nerves or to sleep.

Non-BZP Sleep Agents

Zolpidem tartrate has a very short half-life of 2.5 hours and is effective in the short-term treatment of insomnia (Roth et al., 1995; Lahmeyer et al., 1997). As with the BZPs, chronic administration is not recommended. This agent is being increasingly prescribed in pediatric patients with insomnia despite their being no controlled study in the pediatric population. The non-BZP sleep agent zaleplon is also indicated for the short-term treatment of insomnia in adults (Elie et al., 1999). It should be noted that zaleplon has not been demonstrated to reduce awakenings or increase total sleep time as compared to placebo. Since there have been no controlled studies of these non-BZP sleep agents in children and adolescents, we cannot recommend their use in pediatric populations.

Buspirone

The absence of prominent sedative properties predicts that buspirone would be ineffective for primary insomnia. This was confirmed by Manfredi and colleagues (1991), who tested the hypnotic effectiveness of buspirone in a manner similar to that for BZP hypnotic trials: 4 nights of placebo-baseline, 7 nights of buspirone 10 mg, and 5 nights of placebo-withdrawal. The six adults with chronic insomnia showed a significant *decrease* in total sleep, which was most prominent during the first 3 nights. Similarly, a 3-week course of buspirone was tested by De Roeck and associates (1989) in adult patients with anxiety and insomnia and also yielded no hypnotic effect. Therefore, we do not recommend buspirone for treating primary insomnia in children and adolescents.

Antihistamines

Antihistamines have been used for nearly four decades for mild, rapid sedation. Diphenhydramine is now available without prescription, so its use as a hypnotic agent undoubtedly exceeds physician prescriptions for that purpose. There are fewer controlled trials of antihistamines than of BZPs, but those that are available support their short-term use for transient primary insomnia.

A 50-mg dose of diphenhydramine produces sedation roughly equivalent to that afforded by 100 mg of pentobarbital (Teutsch et al., 1975; Carruthers et al., 1978). In controlled clinical trials, diphenhydramine was found to be superior to placebo in improving sleep latency, number of arousals, and total sleep time (Sunshine et al., 1978; Rickels et al., 1983; Kudo and Kurihara, 1990), while having few effects on the sleep of normal subjects (Borbely and Youmbi-Balderer, 1988). Interestingly, Meulman and associates (1987) found that 50 mg of diphenhydramine was modestly superior to 15 mg of temazepam in improving total sleep time after 5 days of treatment ($p < 0.05$). The only placebo-controlled comparison of an antihistamine and a BZP, this trial was conducted on a small sample of elderly nursing home residents and is, therefore, difficult to generalize to children. Promethazine is also superior to placebo in adult insomniacs (Adam and Oswald, 1986). Hydroxyzine has not been subjected to controlled trial but is probably effective (Schubert, 1984). Like BZP hypnotics, residual morning effects and a reduction in daytime performance tasks are reported and are discussed below (see "Adverse Effects"). Although tolerance to the sedative effects of diphenhydramine has been described (Kudo and Kurihara, 1990), dependence and rebound insomnia have not been described.

Conclusions

Psychophysiological or primary insomnia accounts for an impressive number of hypnotic prescriptions for both adults and children. The majority of these prescriptions are not justified, and an unknown number may produce iatrogenic sleep, anxiety, or drug-dependence problems. However, when transient insomnia is severe and is related to time-limited stressors, both short-acting BZPs and sedating antihistamines effectively improve sleep for at least one week. After that time, tolerance develops to both types of medication. If BZPs are used, the treatment must be short and the medications must be tapered upon discontinuation to minimize rebound insomnia. Because of this additional liability, antihistamines or low-dose, sedating antidepressants are preferable to BZPs for children. However, nonpharmacological measures should be used instead of hypnotic drugs whenever possible and should replace hypnotic drugs within the first 2 weeks of treatment in all cases.

Parasomnias

Parasomnias are defined as abnormal behaviors during sleep, including arousal disorders (sleepwalking, night terrors), sleep-wake transition disorders (sleep talking, leg movements), and rapid eye movement (REM)-associated disorders (nightmares, REM behavior disorder) (Golbin and Sheldon, 1992). Several medications have been reported to exacerbate the syndrome, including neuroleptics,

BZP and non-BZP hypnotics, and tricyclic antidepressants (Glassman et al., 1986; Lauerma, 1991; Golbin & Sheldon, 1992). Case studies have reported both success (Reid et al., 1984) and failure (Cooper, 1987) with diazepam, but no BZP has been systematically studied.

Even if the efficacy of hypnotics were supported in clinical trials, pharmacological treatment is seldom necessary for somnambulism in children. The goal of treatment is to ensure the safety of the child, and this almost always can be achieved by environmental controls, such as locking doors and windows, removing or padding dangerous objects in the child's room, and placing the bed on the ground floor (Linscheid and Rasnake, 1990). Given that any benefit from hypnotics is likely to be short-lived and bears the risk of rebound insomnia, decreased daytime performance, and possible exacerbation of the syndrome, hypnotics are not recommended for sleepwalking in children.

Night Terrors

Night terrors, or *pavor nocturnus*, consist of the sudden onset of intense fear and autonomic discharge, usually taking place during slow-wave sleep. The child screams, is confused and inconsolable, and may cause injury by bolting from his or her bed. The incidence is less than that of somnambulism (3–4% of preadolescents), and the manifestations are more distressing to both parents and children (Golbin & Sheldon, 1992). Environmental measures, supportive psychotherapy, and improved sleep habits are usually sufficient treatment, but short-term hypnotic therapy may be used in severe cases. This use of BZPs has been somewhat better studied than other sleep disorders in children. Diazepam was noted to be successful in one early study (Fisher et al., 1973). More recently, midazolam was evaluated in a single-blind, placebo-controlled study of 15 children with nightly sleep terrors. Midazolam 15 mg at the hour of sleep eliminated terrors in all but one patient and significantly decreased sleep latency and increased total sleep time (Popoviciu and Corfariu, 1983). However, medication was administered for only 2 nights, and its longer-term efficacy is unknown. It is likely that tolerance would occur and that hypnotic therapy of night terrors should be limited to short-term, intermittent courses. More studies with longer follow-ups are required before this can be considered a standard treatment.

Rapid Eye Movement Behavior Disorder

A rare and unusual syndrome that generally appears in adults (Schenck et al., 1987a,b), rapid eye movement (REM) behavior disorder has also been reported in children (Schenck et al., 1986). The syndrome is characterized by the maintenance of muscle tone during REM sleep, causing elaborate, seemingly purposeful, behavior during sleep. Specific behaviors may include the acting out of dreams, self-injury, or violence. The majority of pharmacological trials are un-

controlled adult case series from a single research center, where the syndrome has been successfully managed with clonazepam (Schenck et al., 1989). Tricyclic antidepressants and SSRIs may exacerbate or produce this disorder (Schenck et al., 1992). There is no consensus regarding treatment of its rare occurrence in children.

Aggression

One of the most common uses of sedatives is also one of the least studied. Benzodiazepines, antihistamines, and antipsychotics are all commonly used as “chemical restraints” on an as-needed basis in inpatient psychiatry populations (Vitiello et al., 1987). Although this is a logical application for sedative agents, it has been poorly tested and is not an approved indication for BZPs or antihistamines. Some antipsychotics are approved for this purpose, and these are reviewed in Chapter 12. Buspirone is not used on a p.r.n. basis, but has been tested for the chronic management of aggression. Administration of buspirone’s active metabolite, 1,2-pyrimidinyl piperazine, to rats results in anticonflict activity (Gammans et al., 1986).

Acute Violence

Several open trials have reported success using BZPs for the acute management of aggression in adults (Azcarate, 1975; Monroe, 1975), while others have reported exacerbation of hostility (Dimascio et al., 1969; Bach-y-Rita et al., 1971). There are no controlled studies. Bond and colleagues (1989) reported success with midazolam in two mentally retarded and aggressive adolescents (aged 14–17 years). The medication was given via IM injection in 5 or 10 mg doses and produced rapid calming within 15–20 minutes where other sedative agents (hydroxyzine, amobarbital, and triluopromazine) had failed. Because of the frequency of disinhibitory reactions to BZPs (see “Adverse Reactions”), children are thought to be at higher risk for the exacerbation of agitated states by BZPs (van der Bijl and Roelofse, 1991). However, BZPs do possess some important advantages over antipsychotics as acute sedatives—the incidence of adverse reactions is far lower with BZPs than with antipsychotics, the sedative effects are time-limited with short-acting agents, and the therapeutic index of BZPs is superior. Therefore, for children it is preferable to try BZPs before resorting to sedating antipsychotics for the acute pharmacological management of aggression. Furthermore, it is conceivable that disinhibitory reactions occur at lower doses than effective sedation, suggesting that a multidose, placebo-controlled trial of p.r.n. BZPs would be valuable. Clinically, BZPs such as lorazepam are often administered with antipsychotic medications for treatment of acute violence in efforts to reduce antipsychotic doses and antipsychotic-related side effects, particularly when traditional

neuroleptics are used (see Chapter 12). Examples include severe and repeated aggression in a manic patient or acutely psychotic and violent schizophrenic patient. There are no controlled studies in children and adolescents of combination BZP-antipsychotic for the treatment of acute violence.

After decades of use, diphenhydramine was tested in a small controlled trial for acute agitation in child psychiatric inpatients. Interestingly, Vitiello and associates (Vitiello et al., 1987) found that administering an IM agent to agitated patient had a significant calming effect, but that it did not matter whether this agent was diphenhydramine or placebo. These results further support the need for placebo-controlled trials of acute sedative agents, and the prominent placebo effect suggests that only agents with a very low risk of toxicity should be used. Diphenhydramine will probably cause the least harm, although large doses may produce toxicity. The main risk of using BZPs is the possibility of a disinhibitory reaction. Both are preferable to antipsychotics for children (see Chapter 12).

When traditional high-potency antipsychotics such as droperidol or haloperidol are administered IM to treat acute violence, some clinicians include 25–50 mg of diphenhydramine in the syringe to counter potential extrapyramidal/acute dystonic reactions. There are no data to support this approach, and placebo-controlled studies are warranted to determine whether such combinations reduce the side effects of antipsychotic administration.

Because of its delayed onset of action, there is virtually no role for buspirone in the treatment of acute violence or agitation. Non-BZPs such as zolpidem tartrate and zaleplon are also not indicated in the treatment of acute violent or agitation as there have been no controlled studies in either adults or children.

Chronic Aggression

While as needed (p.r.n.) medication is often necessary for acute management, it would be preferable to prevent aggressive outbursts. Lithium, beta-adrenergic blockers, antipsychotics, and anticonvulsant medications, which are all commonly used for chronic management of aggression, are reviewed in their respective chapters. The development of tolerance to BZPs suggests that they would not be effective over the long term, but neither BZPs nor antihistamines have been systematically tested in the management of chronic aggression.

Ratey and associates (1989, 1991) published promising data on the use of buspirone for aggression in mentally retarded and schizophrenic adults. An open trial reported that low-dose buspirone (15 mg/day) was effective in reducing aggressive and self-abusive behavior in 9 of 14 developmentally disabled adults. Similar effects have been noted in aggressive children with ADHD (Quiason et al., 1991) and autism (Realmuto et al., 1989). Buspirone is being prescribed to aggressive children and adolescents (Mandoki, 1994; Stanislav et al., 1994; Gross, 1995). This effect may be due to buspirone's blocking presynaptic dopa-

minergic receptors when it is prescribed at high doses (Eison and Temple, 1986; Tunnicliff et al., 1992). Buspirone's modulation of serotonergic neurotransmission may account for its possible efficacy in autistic children (Realmuto et al., 1989). More recently, Pfeffer et al. (1997) conducted an open label study of buspirone treatment (up to 50 mg/day) for up to 9 weeks in 25 prepubertal children with anxiety and aggression. Only 3 children showed enough benefit to be continued on buspirone after the study had been completed. Six children actually exhibited an increase in aggression or mania (Pfeffer et al., 1997). Finally, Dunne (1999) reported response rates of 65%–70% in patients treated with buspirone (mean doses 60mg \pm 15mg per day). He reported relatively few side effects with this high-dose buspirone therapy, the most common being increased appetite and weight gain and dissipation of efficacy in some children after 3–4 months of treatment. Gross (1995) conducted an open-label study in 50 children with ADHD and oppositional defiant disorder with normal intelligence with buspirone 15–60 mg/day. ADHD symptoms were helped by anti-ADHD medications (e.g., psychostimulants), but oppositional defiant disorder symptoms remained problematic, which prompted augmentation with buspirone. Approximately 90% of the patients demonstrated improvement in oppositional symptoms with buspirone treatment with specific improvements in self-control, decreased irritability, aggression, and temper tantrums. Although controlled trials are needed to verify these findings, it is reasonable to try buspirone in aggressive children when lithium and beta-adrenergic agents have failed. The risks and side effect profile of buspirone are probably superior to those of anticonvulsants and antipsychotics.

Attention-Deficit Hyperactivity Disorder

Malhotra and Santosh (1998) recently conducted an open clinical trial for 6 weeks of buspirone (0.5 mg/kg of body weight/day; dose range 15–30 mg given in twice-daily dosages) in 12 children 6–12 years of age with ADHD. While four of the ADHD patients had comorbid conduct disorders, none of the subjects had comorbid anxiety disorders or other comorbid conditions. Patients enrolled in this study had failed prior treatment with an adequate dose of a tricyclic antidepressant, parent management, and psychoeducational and cognitive approaches for the ADHD. All patients enrolled in the study had been medication-free for at least 6 weeks. Significant improvement in ADHD symptoms was observed after 6 weeks of therapy. Side effects were minimal and included two subjects reporting mild dizziness during the first week of the study. After the 6-week study period, the medication was stopped with subsequent reemergence of the ADHD symptoms (Malhotra and Santosh, 1998). Thus, buspirone was effective in ADHD patients without comorbid anxiety. There have been no controlled studies of buspirone in ADHD. Such studies are clearly warranted to determine its

role in treating ADHD, particularly since as many as 30% of patients do not respond to standard treatment (e.g., psychostimulants) (see Chapter 7). Moreover, a transdermal patch system for buspirone administration, which permits higher buspirone plasma levels without problematic side effects, is being tested in the treatment of ADHD (Riddle et al., 1999).

BZPs are not indicated for treating ADHD because of their risk of disinhibition. Similarly, non-BZP sleep agents and antihistamines have no role in the treatment of ADHD.

Depression

Several trials of triazolo-BZPs (alprazolam and adinazolam) have suggested that these agents possess an independent antidepressant property, presumably through noradrenergic and serotonergic receptor activity (Greenblatt, 1991b; Kennedy et al., 1991). In depressed adults, combination BZP and antidepressant administration results in more rapid antidepressant response. However, concerns about tolerance and abuse have limited their acceptance for this application. No studies are available that evaluate their use in childhood depression, and they are not currently recommended for this purpose.

Antihistamines and non-BZP sleep agents are also not recommended for use in pediatric depression.

Buspirone has performed favorably in controlled study of major depression in adults (Robinson et al., 1989; Rickels et al., 1991). Preliminary study also indicates that gepirone, a 5-HT_{1A} azapirone partial agonist not available for use in the United States, may be effective in the treatment of atypical depression in adults (McGrath et al., 1994). The serotonergic activity of buspirone and other 5-HT_{1A} azapirone partial agonists make them good candidates for further research in this area, although they are currently unproven as antidepressants in children and adolescents.

Bipolar Disorder

Clonazepam has emerged as a probable antimanic agent in adult studies of bipolar disorder, used either as an adjunct to lithium or as a single agent (Chouinard, 1988; Mauri et al., 1990; Sachs, 1990a,b). However, there is one contrary open trial that was terminated when the first five subjects on clonazepam suffered relapse (Aronson et al., 1989). Lorazepam has also been used successfully (Modell et al., 1985; Lenox et al., 1992), and in one double-blind study it was superior to clonazepam (Bradwejn et al., 1990). However, no comparable studies have been performed on children, and their long-term efficacy must be established in this population before BZPs see widespread use for mania.

CONTRAINDICATIONS

Benzodiazepines

BZPs are absolutely contraindicated only for patients with known hypersensitivity. Most agents are also contraindicated in narrow-angle glaucoma. Relative contraindications include (1) patients with a history of disinhibitory reactions, BZP dependence or abuse, abuse of alcohol or other substances, hepatic dysfunction (for agents that undergo hepatic metabolism); (2) debilitated patients or patients at risk for aspiration; and (3) patients with the acquired immunodeficiency syndrome (AIDS) who are receiving zidovudine (Coffey, 1990; Physicians' Desk Reference, 2001). Due to the muscle relaxant properties of most BZPs, these drugs should also be avoided for patients with symptomatic sleep apnea. Patients must be cautioned against driving or performing dangerous tasks while taking BZPs, especially early in therapy. Similar contraindications are recommended for the non-BZP sleep agents zolpidem tartrate and zaleplon.

Buspirone

Buspirone is contraindicated for patients with known hypersensitivity to the drug. Because of the risk of hypertension and the so-called central excitatory syndrome, it should not be given concurrently with monoamine oxidase inhibitors (MAOIs). Buspirone is relatively contraindicated for patients with hepatic or renal dysfunction (Physicians' Desk Reference, 2001).

Antihistamines

Antihistamines are contraindicated in a variety of situations, depending on their degree of anticholinergic activity. Narrow-angle glaucoma, gastrointestinal (GI) or urinary obstructions, and mental status changes that may be due to anticholinergic toxicity are contraindications to diphenhydramine and cyproheptadine. Most antihistamines potentiate other CNS depressants and analgesics, necessitating caution with these agents. Like BZPs, these agents may cause impairment of driving or work performance and patients must be cautioned against using antihistamines in these situations.

ADVERSE EFFECTS

Benzodiazepines

Sedation

Sedation is the most frequent side effect of BZP use in adults and children (Riddle et al., 1999) and is typically dose-related, resolving when tolerance is achieved

(DuPont and Saylor, 1992). Tolerance to sedation develops rapidly with long-term administration. In children and adolescents, drowsiness may affect school performance.

Decreased Psychomotor and Cognitive Performance

Johnson and Chernik (1982) provided a comprehensive review of performance testing following a single nighttime dose of BZP hypnotic in both insomniac patients and normal volunteers. They concluded that all BZPs decrease next-day performance on a broad range of cognitive and psychomotor tests, depending on the dose and pharmacokinetics of the specific agent. Psychomotor performance may be persistently suboptimal, even throughout long-term BZP treatment (Sakol and Power, 1988). Motor coordination problems, diplopia, tremor, and decreased cognitive performance have also been reported in children on BZPs (Biederman, 1991; Kutcher et al., 1992). In school-age children, cognitive performance is of obvious importance and represents a significant risk of BZP prescription.

Disinhibitory Reactions

A case series by Kraft and associates (1965) reported a paradoxical reaction to chlordiazepoxide in 13 of 130 children treated for diverse psychiatric disorders, with most of these reactions occurring in children with neurological impairment. Commander et al (1991) also reported that three of four children treated with clonazepam who experienced behavioral disinhibition while on the medication had structural brain damage. According to Werry (1982), there is nothing paradoxical about the reaction, since it may be considered an amplification of behaviors normally held in check by social inhibition. Therefore, a more accurate term for this frequent reaction to BZPs is behavioral disinhibition. Beyond the 10% incidence noted by Kraft and colleagues, there are few data in the psychiatric literature on the incidence or risk factors of disinhibitory reactions to BZPs. However, van der Bijl and Roelofse (1991) have reviewed the substantial surgical literature on the phenomenon. They define behavioral disinhibition as an “abolishment of the restraining influence of the cortex [which] has been associated with talkativeness and excitement, depression, agitated toxic psychosis, increased anxiety, hostility and rage.” Anesthesia studies have reported frequencies as high as 23% in children and adolescents undergoing presurgical sedation (Litchfield, 1980; Roelofse et al., 1990). In children, behavioral disinhibition is typically characterized by marked irritability and behavioral temper tantrums (Graee et al., 1994).

Rare Side Effects

Withdrawal seizures occur with unknown frequency but are more common after the abrupt cessation of BZPs with short elimination half-lives. Hallucinations have been reported in rare instances, and recurrent psychosis in response to BZP

treatment has been reported in children (Pfefferbaum et al., 1987a,b). Mania has been described with alprazolam (Arana et al., 1985). Blood dyscrasias, including leukopenia, thrombocytopenia, and agranulocytosis, have been described in adults (Coffey, 1990).

Teratogenicity

There are no prospective studies of in utero exposure to BZPs. Several early studies suggested a relationship between diazepam and birth defects, but these have not been substantiated. A retrospective study of maternal drug history failed to find an increased incidence of birth defects among children born to mothers who received BZPs during the first trimester (Greenberg et al., 1977). Nevertheless, because detailed prospective data are not available, BZPs must be considered potential teratogens, and appropriate contraception should be ensured in women of childbearing age.

Buspirone

Side effects of buspirone and other partial 5-HT_{1A} agonists are relatively mild (Riddle et al., 1999). Buspirone induces less sedation than BZP anxiolytics, but this still remains a possible side effect. Other side effects include dizziness, insomnia, GI upset, lightheadedness, headaches, asthenia, fatigue, anxiety, and irritability or excitement (Riddle et al., 1999). Disinhibition has not been described as such, but excitement might be considered a disinhibitory reaction. There is no known effect on the seizure threshold, nor has there been any report of withdrawal seizures even with chronic administration of these agents (Rakel, 1990). There is also no addictive potential associated with these agents (Murphy et al., 1989). Teratogenicity has not been established, making prevention of pregnancy necessary.

Antihistamines

These medications generally have few serious side effects, although minor side effects can be unpleasant. Sedation and dizziness are most common. Anticholinergic side effects (dry mouth, constipation, urinary retention, blurred vision, confusion) are observed, especially with diphenhydramine and cyproheptadine. Rare, but important, side effects include lowered seizure threshold, hypotension and tachycardia, blood dyscrasias, and GI disturbances. Involuntary-movement disorders have been reported at high doses. There is evidence from animal studies that antihistamines may induce fetal abnormalities, and thus, although there are

no human studies that confirm this, antihistamines should be avoided during pregnancy (Physicians' Desk Reference, 2001).

OVERDOSE

Benzodiazepines

The symptoms of BZP toxicity include drowsiness, ataxia, confusion, slurred speech, tremor, and diplopia. Respiratory depression can occur but is rare. In extreme cases, bradycardia and coma may result. Pfefferbaum and colleagues (1987b) reported two cases of toxicity in children that were characterized by visual and tactile hallucinations and insomnia.

While BZPs are relatively safe when taken alone in overdose and rarely associated with death (Kutcher et al., 1992), they can have additive effects when taken in combination with other CNS depressants including alcohol (Rall, 1990; Green, 1995).

Buspirone

Buspirone toxicity consists of more severe forms of common side effects, especially gastric distress. Miosis is common. No deaths have been reported from buspirone overdose.

Antihistamine

Antihistamine overdose is associated with sedation and hypotension. Diphenhydramine and cyproheptadine, in particular, may cause anticholinergic toxicity and delirium characterized by flushing, dry mouth, fixed and dilated pupils, and confusion. The manufacturers of these agents report that children are more susceptible to hyperarousal with overdose. One large German study examined the clinical symptoms in 136 suicide attempts by diphenhydramine overdose and found that impaired consciousness, catatonic-like stupor, hallucinations, mydriasis, and tachycardia were the most common symptoms (Koppel et al., 1987). The anticholinesterase physostigmine may be used as an antidote to anticholinergic toxicity in severe cases.

ABUSE/DEPENDENCE

Benzodiazepines

A German study estimated that 7% of psychiatric inpatients had abused prescribed medication when not hospitalized, and that 80% of these abused BZPs (Wolf et al., 1989a). Most such abuse took place in a therapeutic situation, with increased incidences among middle-aged women and young men. Alcoholics ap-

pear to be at greater risk for BZP abuse (Ciraulo et al., 1988), and short-acting BZPs are more likely to be abused than are long-acting forms (Wolf et al., 1989a).

While tolerance and dependence are known risks of BZPs in adults, there are no published data in children and adolescents (Salzman, 1989). Nonetheless, guidelines for short-term prescription of BZPs in children and adolescents are similar to adults (Riddle et al., 1999). Gradual tapering of BZPs is recommended as abrupt discontinuation is associated with possible risk of seizure, particularly in patients with a history of seizure, rebound anxiety, increased irritability, headache, fatigue, insomnia, and muscle tension (Salzman, 1990; DuPont and Saylor, 1992; Kutcher et al., 1992; Coffey, 1993) found that tapering clonazepam by less than 0.04 mg/kg per week was safe and effective.

A large epidemiological study from Norway estimated the one-year prevalence of nonprescription BZP use in adolescents to be 10% (ages 13 - 18 years) (Pedersen and Lavik, 1991). Of those who had used BZPs, 87% of boys and 80% of girls reported taking BZPs for intoxication. Pedersen and Lavik (1991) conducted a longitudinal study in 1230 teenagers in Sweden and found that 10% had taken unprescribed anxiolytic and/or sedative hypnotic agents during the past year. The most common explanations for taking these agents included problems with sleep, depression, and other life stressors. It should be noted that 2/3 of the adolescents were actually given BZPs by their parents, most commonly their mothers (Pedersen and Lavik, 1991). Thirteen percent of male adolescents and 20% of female adolescents reported taking BZPs for intoxication. Teenage use was highly correlated with parental use, which suggested that the adolescents were modeling the medication use observed in their parents. Equivalent data for the United States are not available.

The American Psychiatric Association has determined that although most BZP abuse is by individuals with a history of opiate, sedative, or alcohol abuse, the prolonged prescription of BZPs increases the risk of dependence in all patients (Salzman, 1991). For these reasons, patients with a history of substance abuse should not be prescribed BZPs, and all prescriptions should be monitored for escalation of doses. Caution is also required in children or adolescents with a strong family history of substance abuse or dependence. The appropriate administration of BZPs in child and adolescent psychiatric disorders is almost always short, as discussed above.

Risks for abuse and dependence should be considered similar for non-BZP sleep agents such as zolpidem tartrate and zaleplon.

Buspirone

Buspirone was initially marketed as an anxiolytic without significant sedation or abuse potential, based on animal studies. Clinical experience thus far is consistent

with this claim. No significant withdrawal syndrome has been described, even after abrupt cessation, and no cases of abuse have been reported (Balster, 1990).

Antihistamines

Tolerance to the sedative effects of antihistamines have been described, and with tolerance comes the concern about potential dependence and abuse. However, antihistamines have few reinforcing effects and several unpleasant side effects. Diphenhydramine is available without prescription and is not considered a drug of abuse. One study reported sedative abusers rated 600 mg of diphenhydramine as pleasurable, but only 5 of the 10 subjects could tolerate the dose (Wolf et al., 1989b). Therefore, the abuse potential of antihistamines may be considered low.

DRUG INTERACTIONS

See Table 5.

AVAILABLE PREPARATIONS AND COSTS

See Tables 1 and 2.

INITIATING AND MAINTAINING TREATMENT

Benzodiazepines

Since the efficacy of BZPs in children and adolescents has not been established, neither have precise clinical guidelines for their use. No specific medication laboratory evaluation is recommended. As with most medications, preadolescent children generally require more frequent doses than adolescents or adults because of their higher rates of hepatic metabolism. Coffey (1990) has published dosing guidelines for BZPs based on clinical experience, and the recommendations in Table 6 are based on these guidelines, as well as on the studies cited above. The 0.25 mg tablet of alprazolam is scored, allowing for a starting dose for preadolescent children of 0.125 mg b.i.d for panic disorder. For sleep induction, a reasonable dose of short-acting hypnotics is one-half the adult starting dose for preadolescent children and the lower limit of the adult dose for adolescents. Long-term efficacy has not been demonstrated in children and adolescents for either indication, so the course of treatment should be short—less than 30 days for panic disorder and less than 2 weeks for insomnia.

We do not recommend using non-BZP sleep agents at present given the lack of study in children. Many clinicians use zolpidem tartrate (Ambien) for

TABLE 5 Drug Interactions with Anxiolytics and Sedatives

Benzodiazepines	<p>Drug whose activity or blood levels may increase:</p> <ul style="list-style-type: none"> alcohol sedatives (narcotic, analgesic, recreational) TCA's phenytoin zidovudine <p>Drugs that may increase the activity of benzodiazepines:</p> <ul style="list-style-type: none"> antimicrobials (erythromycin, isoniazid) oral contraceptives cimetidine alcohol sedatives neuroleptics MAOIs <p>Drugs whose activity may be impaired:</p> <ul style="list-style-type: none"> carbamazepine <p>Drugs that may decrease the activity of benzodiazepines:</p> <ul style="list-style-type: none"> antacids <p>Drugs that may produce adverse reactions:</p> <ul style="list-style-type: none"> MAOIs (central excitatory syndrome)
Buspirone	<p>Drugs whose activity or blood levels may increase:</p> <ul style="list-style-type: none"> neuroleptics (theoretical and one report of increased haloperidol levels) <p>Drugs that may produce adverse reactions:</p> <ul style="list-style-type: none"> trazodone (one report of hepatic toxicity) MAOIs (theoretical risk of central excitatory syndrome) neuroleptics (theoretical risk of increased effects of dopamine antagonism)
Antihistamines	<p>Drugs whose activity or blood levels may increase:</p> <ul style="list-style-type: none"> alcohol sedatives (narcotic, analgesic, recreational) <p>Drugs that may produce adverse reactions:</p> <ul style="list-style-type: none"> potentiation of anticholinergic side effects and possible toxicity with any anticholinergic agent

children with sleep disturbances, typically starting with doses of 5 mg at bedtime and not exceeding a dose of 10 mg.

Buspirone

Buspirone is likewise without guidelines for children and is not approved for use under the age of 18 years. Coffey (1990) suggests titrating up to 20 mg/day in

TABLE 6 Suggested Agents and Dosing Guidelines for the Use of Anxiolytic Agents in Children and Adolescents

Indication	Suggested agents	Starting dose			Maximum daily dose	
		Preadolescent	Adolescent	Adolescent	Preadolescent	Adolescent
Panic disorder	Alprazolam	0.125 mg b.i.d. or t.i.d.	0.25 mg b.i.d. or t.i.d.	1–4 mg	8–10 mg	
	Clonazepam	0.25 mg q.d.	0.5 mg q.d.	0.1–0.2 mg/kg ^a	0.1–0.2 mg/kg ^a	
Anticipatory anxiety	Alprazolam	0.125–0.25 mg	0.25–0.5 mg	NA	NA	
	Diphenhydramine	25–50 mg	50–100 mg	5 mg/kg	5 mg/kg	
Generalized anxiety disorder, separation anxiety disorder	Hydroxyzine	0.6 mg/kg	0.6 mg/kg	NA	NA	
	Buspirone	2.5 mg b.i.d.	5 mg b.i.d.	20 mg/day	60 mg/day	
Insomnia	Diphenhydramine	25–50 mg	50–100 mg	5 mg/kg	5 mg/kg	
	Any short-acting Hypnotic	50% of adult starting dose	Lower limit of adult dose	50% of adult maximum	Adult maximum	

^a Dose is the maximum recommended for seizure disorders; maximum for psychiatric indications is not established.

divided doses for adolescents and 5–10 mg/day in divided doses for preadolescents for the treatment of generalized anxiety disorder. The 5 mg tablet may be cut to allow for increments of 2.5 mg. Ratey and colleagues (1989,1991) have suggested that the optimal daily dose of buspirone for the treatment of aggression may be lower than for anxiety. They found 15 mg/day to be optimal in aggressive adults, with some loss of effect at higher doses, as compared with 30–60 mg/day commonly reported for adult anxiety disorders. Therefore, the optimal dose for the treatment of chronic aggression in children may also be low. Effective dose ranges of buspirone for ADHD have been reported to range from 15 to 30 mg/day given in divided doses twice per day (Malhotra and Santosh, 1998). Typical starting doses of buspirone are 5 mg t.i.d. and then titrating it gradually to 30, 60, and 90 mg/day using a t.i.d. dosing regimen targeting the lowest dose with maximal efficacy (Riddle et al., 1998). Compliance may be problematic with this dosing strategy as compliance is more often facilitated when medication can be taken one time per day. Should the buspirone transdermal patch system prove efficacious and safe, this may represent an alternative that might allow for better compliance.

Antihistamines

There is little or no evidence supporting the use of antihistamines in the treatment of anxiety disorders. The two most appropriate indications are insomnia and situational or anticipatory anxiety. These situations require single doses or very brief courses of treatment, the dosing guidelines for which appear in Table 6.

MANAGEMENT OF SPECIFIC SIDE EFFECTS

Benzodiazepines

Behavioral Disinhibition and Overdose

There is no specific treatment strategy for BZP-induced behavioral disinhibition. Supportive and behavioral management may be sufficient while the symptoms abate. In the emergency setting, a drug history and laboratory screen should be performed to rule out concurrent alcohol or other substance use adding to the syndrome (Coffey, 1990). Physostigmine has been used by anesthesiologists to treat BZP-induced delirium, such as the BZP antagonist flumazenil. However, these are by no means established treatments and should not be used to treat behavioral disinhibition (van der Bijl and Roelofse, 1991). In massive overdose or when other CNS depressants are present in the system, respiratory and cardiac support may be required.

Sedation and Decreased Cognitive Performance

These effects of BZPs are of great importance in children and adolescents and require careful ongoing assessment. Tolerance may develop to sedation, but not

to cognitive and psychomotor deficits. Since there is no specific treatment, minimizing the doses and length of treatment is necessary. Families should be intimately involved in weighing the benefits of the medication against the risk of academic or social delay. If used for sleep, the effect on next-day performance may be minimized by using short-acting agents.

Buspirone

The side effects of buspirone are seldom serious but, if intolerable, may require a reduction in dose or cessation of treatment. Dizziness, GI upset, and headaches are common reasons for discontinuing treatment. Gastrointestinal symptoms may be relieved by giving doses with meals. Headaches, if infrequent, may be managed with acetaminophen.

Antihistamines

If anticholinergic effects predominate, consideration may be given to an alternative agent with fewer anticholinergic properties. Since these medications are appropriate only for very short-term uses, side effects are generally tolerable, if potentially unpleasant. Apart from reducing the dose or discontinuing treatment, there is no specific therapy for antihistamine side effects.

WITHDRAWING MEDICATION

Benzodiazepines

Several strategies for the withdrawal of BZP treatment have been advocated. Single-dose or intermittent single-dose prescription may require no special withdrawal program, but patients should be monitored closely for rebound insomnia even in these cases. With longer treatment, withdrawal symptoms can include insomnia, anxiety, tremulousness, diaphoresis, irritability, muscle cramps, tinnitus, and nausea. Therefore, moderate or long-term BZP use necessitates a gradual tapering of dosage. If treatment has been chronic, this tapering schedule may take weeks or months (Coffey, 1990). Since the risk of severe withdrawal is greatest with short-acting agents, it may be useful to switch to long-acting agents such as diazepam or clonazepam at equivalent potency before tapering the drug (Busto et al., 1986). One double-blind, placebo-controlled study of carbamazepine administered during gradual tapering of long-term BZP yielded a higher success rate and milder withdrawal symptoms among adult patients who had a history of dependence (Schweizer et al., 1991).

Buspirone and Antihistamines

No withdrawal syndromes have been described for these agents, and, therefore, discontinuation does not usually require a tapering schedule. However, it may

be prudent to discontinue buspirone and antihistamines gradually, since experience with these agents in children is still limited.

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16

Adrenergic Agents in Child and Adolescent Psychiatry

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CLONIDINE AND GUANFACINE

Clonidine and guanfacine, α_2 -adrenergic agents with known antihypertensive efficacy, have no established FDA indications for use in child and adolescent psychiatry. Because they activate presynaptic α_2 receptors, which through their negative feedback action cause postsynaptic inhibition of central noradrenergic neurons, clonidine and guanfacine may be particularly useful agents in psychiatry. They are currently under active investigation to better discern their role in the treatment of children and adolescents. Thus far, they have been most studied with regard to Tourette's disorder, attention-deficit hyperactivity disorder (ADHD) in children and adolescents, and the control of opiate withdrawal symptoms (primarily clonidine). Indeed, clonidine has been recognized as an effective antihypertensive agent in adults since the 1960s (Wilber, 1980), while Leckman and Cohen (1983) and Hunt et al. (1985) extended its use to pediatric ADHD patients with and without Tourette's disorder for whom stimulants were contraindicated, ineffective, and/or associated with problematic side effects. Swanson et al. (1995) reported that by the early 1990s, about 200,000 prescriptions were

being written for clonidine (0.05–0.1 mg in multiple doses throughout the day) for pediatric patients with ADHD (Hunt et al., 1990) and patients with sleep disturbances (stimulant-related and unrelated) (Rubinstein et al., 1994; Wilens et al., 1994).

Clonidine appears to be most effective in reducing hyperarousal states with high levels of motoric activity and arousal and less effective in ameliorating distractibility and impaired attention span (Riddle et al., 1999). In contrast, guanfacine may be effective in reducing both hyperarousal states and impaired attention span (Arnsten et al., 1996). The total number of children and adolescents who have participated in controlled studies is still too small to declare an outcome. Controlled studies of clonidine (reviewed below) have been somewhat contradictory, while a recent double-blind, placebo-controlled study of guanfacine suggests potential efficacy and safety in pediatric patients with ADHD and Tourette's syndrome. In the meantime, many clinicians employ empirical trials of clonidine despite the lack of established criteria for patient selection or efficacy in children and adolescents.

Chemical Properties

Clonidine and guanfacine (Fig. 1), through their agonistic effects on presynaptic α_2 -adrenergic receptors, affect the locus ceruleus, the major noradrenergic center in the brain, resulting in a decrease in the amount of neurotransmitter released from the nerve terminal (Svensson et al., 1975; Hunt et al., 1988). Guanfacine is longer acting than clonidine and is also more selective for postsynaptic α_2 -

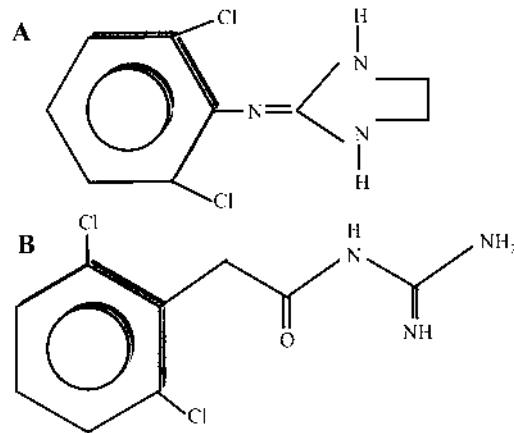


FIGURE 1 (A) Molecular structure of clonidine. (B) Molecular structure of guanfacine.

adrenergic receptors in prefrontal cortex (Table 1). These two properties are believed to account for guanfacine's lower risk of sedation and beneficial effects on attention (Arnsten et al., 1996).

Clonidine

Oral clonidine is rapidly and almost completely absorbed from the GI tract (Hunt et al., 1990). Peak plasma concentrations are obtained within 1–3 hours. Since it is so lipophilic, clonidine easily crosses the blood-brain barrier. It has no active metabolites, with 35% metabolized in the liver and 65% excreted unchanged in the urine (Kaplan and Sadock, 1991). Its elimination half-life is 8–16 hours. Clonidine's peak behavior effects are observed 2–6 hours after its administration and are associated with reduced sympathetic and increased parasympathetic activity, which results in decreased blood pressure, pulse, and salivation (Riddle et al., 1999). Sedation effects are most prominent 30–90 minutes after the last dose of clonidine. This is in contrast to its antihypertensive and cardiac effects, which begin within a half to one hour of ingestion and last for 6–8 hours (Hunt et al., 1990). Correlation of oral or skin patch clonidine dose with serum drug levels has not been established (Hunt et al., 1988, 1990).

In addition to being available in an oral form, clonidine is also available as a skin patch known as the transdermal system. Absorption is a function of the surface area of the patch, while the plasma concentration of clonidine depends on the patient's renal function—specifically, the creatinine clearance (Hunt et al., 1990). In children, the behavioral effects are often noted within 2–3 days of applying the skin patch; this corresponds to its maximal antihypertensive effect, which also occurs 2–3 days after it is initiated (Hunt et al., 1988, 1990).

Guanfacine Hydrochloride

Guanfacine's plasma half-life is approximately 17 hours. Peak plasma levels occur within 2–3 hours of administration, and steady-state blood levels are typically achieved within 4–5 days (see Table 1).

Indications

For indications for use of clonidine and guanfacine, see Table 2.

Tourette's Syndrome

Chapter 7 presents a description of this disorder. For an excellent discussion of the pharmacological treatment of tic disorders, the reader is referred to the comprehensive review by Scahill and colleagues (2000).

Clonidine is the most frequently prescribed agent for this condition although its efficacy for treating Tourette's syndrome remains to be determined

TABLE 1 Pharmacokinetics of Adrenergic Agents in Children and Adolescents

Generic name (brand name)	Selectivity	Peak plasma concentration (hr)	Plasma half-life (hr)	Metabolism and excretion	Comments
Clonidine (Catapres)	α_2	2–6	8–12	35% hepatic and 65% renal	Very lipophilic; easily penetrates blood-brain barrier
Guanfacine (Tenex)	α_2	1–4	17 (10–30)	Renal	May be better tolerated by children and adolescents than clonidine with fewer side effects
Propranolol (Inderal)	β_1 and β_2	1–1 ¹ / ₂	4	Hepatic	Very lipophilic; potent central and peripheral effects
Atenolol (Tenormin)	β_1 (higher doses affects α_2 also)	2–4	6–7	Renal	May be better tolerated than propranolol by children with fewer side effects

TABLE 2 Indications for Clonidine and Guanfacine in Psychiatry

FDA-approved indications:

None

Likely indications:

Tourette's disorder (guanfacine > clonidine)

ADHD

ADD without hyperactivity (guanfacine only)

ADHD treated with psychostimulant (guanfacine > clonidine)

Sleep problems (spontaneous or stimulant-induced in ADHD) (clonidine > guanfacine)

Possible indications:

Anxiety and panic disorders

Hyperactivity in developmental disorders (e.g., autism, fragile X syndrome)

Psychosis

Akathisia (adjunctive only)

ADHD in adults (guanfacine > clonidine)

Social phobia

PTSD

(Freeman et al., 2000). A survey of over 4,800 cases worldwide found that clonidine was the most prescribed drug for the monotherapy of Tourette's syndrome (Freeman, personal communication, 2001). For polypharmacy, clonidine was the second most prescribed drug (50% of 1,040 cases vs. 76% of 1,040 for haloperidol) (Freeman, personal communication, 2001). It should be noted that many practicing clinicians choose to start with clonidine or guanfacine when medication is required in the treatment of Tourette's syndrome to avoid the serious and sometimes irreversible side effects associated with antipsychotic use, such as tardive dyskinesia. This preference appears to have decreased over the past few years as practitioners have become more experienced with using atypical neuroleptics which may have a more benign side effect profile than traditional antipsychotics (e.g., haloperidol).

Case History

A 9-year-old boy with ADHD who had been started on methylphenidate by his pediatrician subsequently developed multifocal tics and was referred to child psychiatry for evaluation. He was observed to have a combination of vocal and motor tics. The latter often disrupted the classroom. Coprolalia was also prominent. His parents and personnel at the school he attended were quite upset because, since being started on methylphenidate 9 months earlier, he had exhibited a marked improvement in behavior. His tics had started 3 months prior to the psychiatric evaluation while on a dose of methylphenidate 15 mg t.i.d. The dose had been

lowered to 10 mg t.i.d. without improvement in tic behavior. The medication was subsequently discontinued. Unfortunately, the patient's tics continued unabated and his ADHD behavior recurred while he was off stimulant medication. A family history revealed a significant positive history of tics in two maternal uncles and one maternal grandfather. There was no history of seizure disorder. Neurological examination of the patient was unremarkable except for periodic tics and vocalizations. An EEG was completely normal. In view of the patient's combined ADHD and probable Tourette's disorder, pharmacological intervention was proposed. The treating psychiatrist was reluctant to prescribe an antipsychotic such as haloperidol or risperidone as they do not have demonstrated efficacy in ADHD and because of their potential side effects. A test dose of clonidine of 0.05 mg (one-half tablet) at bedtime was the initial starting dose. After tolerating this dose without side effects, his dose was increased to 0.05 mg b.i.d. It was increased by a 0.05 mg increment every 5 days to an ultimate dose of 0.05 mg at 8 a.m., 12 noon, and 4 p.m. and 0.1 mg at 8 p.m., at which he experienced a marked reduction of tic behaviors and a moderate improvement in ADHD behaviors. One year later, given his marked improvement, clonidine was tapered by 0.05 mg increments every 7 days and discontinued. However, the patient subsequently relapsed with exacerbation of ADHD symptoms and reemergence of tics. His parents were particularly concerned because of the teacher and school reports detailing problematic behavior that was interfering with their son's performance in school. The psychiatrist and parents decided to treat the symptoms with guanfacine, particularly in view of the patient's problems with attention and focusing on school work. A test dose of guanfacine 0.5 mg (one-half tablet) at bedtime was the initial starting dose. Careful monitoring for orthostasis, sedation, and other side effects ensued. After tolerating the 0.5 mg test dose for one week, his dose was increased to 0.5 mg b.i.d. It was increased by 0.5 mg increments every 5 days to an ultimate dose of 1 mg t.i.d., at which he experienced a significant reduction in tic and ADHD behaviors without problematic side effects.

Clonidine. Uncontrolled studies of clonidine for tics have yielded somewhat contradictory findings. Comings et al. (1990) found that transdermal clonidine administration resulted in "some improvement in 61% of 210 patients with Tourette" syndrome. In contrast, Steingard et al. (1993) reported a significant improvement in ADHD symptoms but not tics in 7 patients with ADHD and comorbid tic disorder with clonidine doses of 0.1–0.3 mg/day. When comparing clonidine treatment with haloperidol treatment in 22 patients with Tourette's syndrome, it was found that clonidine decreased tic symptoms in 68% of those studied (Borison et al., 1983). Clonidine has also been reported to be effective in decreasing symptoms of tic disorder during haloperidol's withdrawal (Max and Rasmussen, 1986).

Clonidine has also been reported to be useful in augmenting the efficacy of neuroleptics in the treatment of Tourette's disorder, and it may allow for using lower doses of neuroleptics, which may decrease the risk of developing undesirable side effects (Bruun, 1984; Max and Rasmussen, 1986).

Truong and colleagues (1988) studied 81 patients with multifocal tic disorders who were treated with haloperidol, clonazepam, or clonidine. They found that haloperidol was more effective than clonazepam, which was more effective than clonidine. Because of the severe adverse effects associated with typical antipsychotics, particularly tardive dyskinesia, these authors recommended that clonazepam be used as the initial treatment for these tics, followed by a combination of clonazepam and clonidine as a next step when necessary (Truong et al., 1988). There are, however, drawbacks with using clonazepam (see Goetz, 1992; Graae et al., 1994). Traditional neuroleptics are best used as the last line of treatment when all else has failed and only after it has been determined that the tic symptoms are significantly problematic and outweigh the risks inherent with neuroleptic use.

There has also been the suggestion that clonidine may be particularly effective in certain subgroups of patients (Cohen et al., 1980; Singer et al., 1986; Steingard et al., 1993b; Bond, 1986). Mesulam and Peterson (1987) reported that it may be particularly helpful in patients with mild tics and obsessive-compulsive symptoms—symptoms not infrequently associated with Tourette's syndrome. Clonidine may also be helpful for the treatment of concomitant Tourette's disorder and disruptive behavior disorders, such as ADHD. When clonidine is effective in controlling tic behavior, its discontinuation has been shown to result in the reemergence and/or worsening of the tics, which are ameliorated when the medication is reintroduced (Singer et al., 1986; Erenberg, 1988).

Controlled studies evaluating the efficacy of clonidine for Tourette's syndrome have also produced conflicting findings. Borison et al. (1982) and Goetz et al. (1987) were unable to confirm Cohen et al.'s (1979) hypothesis that clonidine was an effective treatment for Tourette's syndrome. More recently, Leckman and colleagues (1991) conducted a double-blind, placebo-controlled study in pediatric patients with Tourette's syndrome treated with clonidine 0.25 mg/day. Twenty-four patients received clonidine and 23 patients received placebo. Fifty percent of the Tourette's syndrome patients had comorbid ADHD. Clinician ratings revealed a significant improvement in tics but not in ADHD symptoms in patients treated with clonidine vs. placebo, whereas parent ratings noted a significant decrease in ADHD symptoms but no significant improvement in tic symptoms. Gunnings (1992) conducted a double-blind, placebo-controlled study in children with ADHD and comorbid Tourette's syndrome. Patients were treated with clonidine 0.03–0.05 mg/kg/day ($n = 16$) or placebo ($n = 16$) for 8 weeks. Clonidine was not found to be superior to placebo for reduction of tics. In fact,

31% of patients treated with placebo exhibited a reduction in tics, whereas 25% of patients treated with clonidine exhibited a reduction in tics. In a double-blind, placebo-controlled crossover trial of clonidine (0.05 mg four times per day), desipramine, and placebo in 34 children with Tourette's syndrome and ADHD, clonidine was no more effective than placebo in reducing ADHD and tic symptoms as per parent ratings (Singer et al., 1995). Surprisingly, patients treated with desipramine did exhibit a significant reduction in both tics and ADHD symptoms. In view of both open-label and four of five placebo-controlled studies of clonidine not demonstrating it to be more effective than placebo, we do not recommend its routine use as an effective treatment for tics, particularly as a first-line treatment. Given the waxing and waning nature of tics, there is added reason to be cautious in medication management. When medication is indicated for tics, clonidine is recommended only after other medications (e.g., guanfacine, clonazepam, atypical neuroleptics) have failed.

A recent multicenter study of 140 patients with ADHD and a chronic tic disorder compared clonidine, methylphenidate, combination methylphenidate-clonidine, and placebo (Tourette Syndrome Study Group, Principal Investigator Kurlan R, In press). Both clonidine and methylphenidate reduced tic and ADHD symptoms with the combination resulting in the biggest reduction in symptoms. Clonidine and methylphenidate demonstrated equal efficacy in treating ADHD symptoms. While clonidine treatment appeared to result in greater reductions in tic severity, this was not statistically significant. Clonidine was most helpful for disruptive, impulsive behavior, whereas methylphenidate did differentially better for attentional problems. No cardiac problems were noted with either agent. The most common side effect with clonidine treatment (medium dose 0.1 mg t.i.d.) was sedation. A similar multicenter study has been proposed using guanfacine. The results of this study have not yet been presented.

Guanfacine. In an open trial of guanfacine treatment of 1.5 mg/day for 1–5 months in 10 children with Tourette's syndrome and ADHD, Chappell et al. (1995) reported a reduction in phonic tics but not motor tics as measured by clinician ratings. In contrast, parent ratings showed exactly the opposite—a reduction in motor but not phonic tics. Scahill and colleagues (2001) conducted an 8-week randomized, double-blind, placebo-controlled study of guanfacine in 34 medication-free children and adolescents 7–14 years of age with comorbid ADHD and tic disorder. A decrease in tic severity (31%) as measured by The Total Tic Score of the Yale Global Tic Severity Scale was observed in patients treated with guanfacine. In contrast, a 0% decrease in tic severity was observed in patients treated with placebo. It should be noted that in these patients tics were generally mild and not the primary target of treatment. The medication was well tolerated with no significant decreases in heart rate or blood pressure. Only one

subject treated with guanfacine withdrew from the study because of problematic sedation. Guanfacine may be better tolerated than clonidine with fewer side effects, particularly sedation.

In contrast with other clinicians, when child and adolescent psychiatrists are referred a patient with Tourette's disorder, it is not uncommon for there to be concomitant psychiatric problems, such as ADHD, obsessions and compulsions, sleep disturbances, depression, or conduct disorder (Golden, 1986; Janakovic and Rohaidy, 1987). Clonidine and methylphenidate have been used together to treat Tourette's disorder with coexistent ADHD or refractory ADHD (Hunt et al., 1988, 1990; Connor, 2000) (see below). Guanfacine and methylphenidate combinations are also increasingly being administered.

ADHD in Children and Adolescents

Clonidine. Currently, clonidine is considered an investigational medication in the treatment of ADHD in children and adolescents. In an open-label trial of eight children with ADHD, Hunt (1987) found that oral clonidine treatment up to 5 µg/kg per day for 2 months followed by change to transdermal clonidine patch at the equivalent dose was as effective as methylphenidate based on parent, teacher, and clinician ratings of behavior. In contrast to the parents and clinicians, who expressed no preference for one medication over the other, the teachers appeared to slightly prefer the effects of methylphenidate over clonidine. Hunt (1987) also found that despite the relatively common occurrence of at least transient sedation when clonidine was used to treat ADHD, children have reported feeling more "normal" on clonidine than on methylphenidate. Hunt (1987) found in this same study that the transdermal patch form of clonidine was as effective as oral clonidine. Seventy-five percent of the children and families involved in the study preferred the skin patch to oral administration because it avoided the embarrassment of having to take pills at school and was more convenient (Hunt, 1987). In a retrospective chart review of 54 ADHD children with and without comorbid tic disorders treated with open-label clonidine, Steingard et al. (1993a) reported improvement in both ADHD symptoms (72%, 39/54) and tic symptoms (75%, 18/24). Patients with comorbid tic disorders appeared to exhibit greater reduction in behavioral disturbances (23/24, 96%) than ADHD patients without a comorbid tic disorder (53%, 16/30) (Steingard et al., 1993a).

Hunt and colleagues (1985) conducted an 8-week, double-blind, placebo-controlled study of clonidine 4–5 µg/kg/day in 10 pediatric ADHD patients. Typical clonidine doses were 0.05 mg administered four times per day or 0.2 mg/day. Clonidine was found to be superior to placebo in the treatment of disruptive behavior in these children by parent, teacher, and clinician ratings of behavior. In a double-blind, parallel-group study of three groups of 24 pediatric ADHD patients treated for 2 months with clonidine (0.03–0.05 mg/kg/day), methylphen-

idate (0.03–0.05 mg/kg/day), or placebo, Gunning (1992) reported significantly greater improvement in ADHD symptoms in patients treated with clonidine or methylphenidate than in patients treated with placebo. Fifty percent of patients treated with methylphenidate or clonidine vs. 13% of patients treated with placebo were rated as clinically improved by a psychiatrist. As compared to placebo, significantly greater reductions in parent and teacher ratings of ADHD were observed in patients treated with clonidine (approximately 14%) and methylphenidate (approximately 20%). It should be noted that in this study rates of response to psychostimulants was lower (50%) than is typically reported (Riddle et al., 1999).

Thus, it is critical to identify particular populations of patients who may be most likely to have favorable response to clonidine. The most clonidine-sensitive children appear to be those with a high level of motoric overactivity, coexistent oppositional or conduct disorders, and early onset of their symptoms (Hunt et al., 1988, 1990). Clonidine decreases motor overactivity and hyperarousal states and may improve frustration tolerance in these children. This often leads to their increased compliance with commands and expectations and significantly improved task performance, resulting in better learning and improved grades (Hunt et al., 1988, 1990). Clonidine does not appear to be effective for children with ADHD whose primary problem is distractibility and impaired attention span (Hunt et al., 1986). Psychostimulants and perhaps guanfacine (see below) appear to be more effective than clonidine in ameliorating distractibility and attention difficulties. Clonidine is also not effective in the treatment of ADD without hyperactivity, where distractibility and poor attention span are the most prominent symptoms (Hunt et al., 1988, 1990). In contrast, the psychostimulants and guanfacine can be effective for this condition.

As mentioned, clonidine may be particularly effective in children and adolescents with coexistent oppositional or conduct disorders. It has been shown to decrease physical and verbal aggression in nonpsychotic adolescents (Hunt et al., 1988, 1990). This is likely due, at least in part, to its sedating properties, which may also be why it has been found to be effective in other patient populations, such as manic patients with extreme hyperarousal. In contrast to methylphenidate, which is believed to affect primarily the dopaminergic system (which may play a key role in the ability to attend), clonidine is believed to affect primarily the noradrenergic system (thought to play an important role in arousal) (Hunt et al., 1988, 1990). This may explain the fact that teachers more often prefer methylphenidate to clonidine, since sedation might hinder classroom performance in spite of decreased disruptive behavior. In fact, Hunt (1985) found that clonidine's most common side effect was sedation, which usually appeared one hour after it was dispensed and lasted for as long as an hour. Fortunately, tolerance to this effect appears to occur within 3 weeks, so that discontinuation of the medication is seldom necessary (see "Side Effects").

The total number of children and adolescents enrolled in controlled studies is still too small to declare a definitive outcome. Certain symptom clusters that are common in ADHD children do appear to be more amenable to treatment with clonidine. While clonidine may be effective in treating ADHD characterized by hyperarousal states with increased motor activity, low frustration-tolerance states, and coexistent oppositional and conduct disorders, and in those who have responded poorly to CNS stimulants, it is not effective in the treatment of oppositional and conduct symptoms not associated with ADHD, nor is it useful in the treatment of distractibility in nonhyperactive ADD (Hunt et al., 1988, 1990). Therefore, clonidine and stimulants may be useful for different groups of patients with ADHD (Hunt, 1987).

Combination Therapy. Some individuals do seem to respond best when treated with a combination of methylphenidate and clonidine (Hunt et al., 1988, 1990), and this combination is often used to treat children with ADHD (Riddle et al., 1999). This regimen is typically considered in children and adolescents whose symptoms do not respond sufficiently to either medication when used alone. When distractibility and hyperarousal states coexist, this combination may be particularly efficacious (Hunt et al., 1988, 1990). The approach is best achieved when methylphenidate dosages are gradually adjusted after the patient is on a stable dose of clonidine (Hunt et al., 1988, 1989, 1990). One notable advantage of this combination is that it may result in a reduction of the methylphenidate dose, while the side effects are usually minimal and may be better tolerated than when the medicines are used by themselves (Hunt et al., 1988, 1990; Comings et al., 1990). Also, this combination has been shown to have a greater effect on parent ratings of aggressive children than does either medication when used alone (Hunt et al., 1988, 1990).

Dr. Floyd Sallee (principal investigator) has recently been funded by the NIH to conduct a multicenter controlled study in children with primary ADHD comparing the efficacy and safety of clonidine, methylphenidate, and clonidine-methylphenidate combination therapy (F. Sallee, personal communication). When completed, the study will provide critical information on the safety and efficacy of monodrug therapy vs. combination therapy as well as risk for developing tics with each treatment condition.

Guanfacine. Open-label studies suggest that guanfacine may be effective in reducing both hyperactivity and attention disturbances in ADHD (Hunt et al., 1995; Chappell et al., 1995; Horrigan and Barnhill, 1995). Guanfacine is thought to have a selective effect on attention (Arnsten et al., 1996). Scahill and colleagues (2000) reported on 34 medication-free pediatric patients, 7–14 years of age, with comorbid ADHD and tic disorder. A mean improvement of 37% on the ADHD Rating Scale was observed in patients treated with guanfacine, while an 8% mean improvement was observed in patients treated with placebo. Blind

ratings revealed that 9 of 17 patients treated with guanfacine were considered to be “much improved or very much improved,” while 0 of 17 patients treated with placebo were rated as “much improved or very much improved.” However, no significant differences in improvement as measured by the Hyperactivity Index on the Parent Conners Questionnaire (HI) were observed between patients treated with guanfacine (27% reduction) vs. those treated with placebo (21% reduction). The Vigil Continuous Performance Task (CPT) was also administered during the study as an index of attention. Patients treated with guanfacine performed significantly better on the CPT task than those treated with placebo. Both commission and omission errors on this task decreased significantly in patients treated with guanfacine (22% and 17%, respectively), while in the placebo group, commission errors increased by 29% and omission errors increased by 31%.

Guanfacine appears to be better tolerated than clonidine in the treatment of ADHD and Tourette’s syndrome with fewer problematic side effects, particularly sedation. Moreover, guanfacine may also be more effective in ameliorating inattentiveness and distractibility, while clonidine is typically effective in reducing motoric hyperactivity but ineffective in improving attention and distractibility. Therefore, we recommend considering clonidine use only after guanfacine has been demonstrated to be insufficiently effective for ADHD, Tourette’s syndrome, or comorbid ADHD–tic disorders. While guanfacine may be helpful in treating ADD without hyperactivity, we do not recommend clonidine’s use for this condition. Moreover, we advise using guanfacine-stimulant combinations before trying clonidine-stimulant combinations in ADHD patients. The rare but potentially severe cardiotoxic effects of clonidine-methylphenidate combinations (Cantwell et al., 1997) have not thus far been reported for guanfacine-methylphenidate combinations.

ADHD in Adults

Methylphenidate has been shown to be effective in the treatment of ADHD throughout life (Wender, 1987). Since the most prominent symptoms in adults tend to be poor attention focus and distractibility rather than hyperactivity, study of guanfacine is warranted, whereas clonidine may be less effective for this population (Hunt et al., 1988, 1990).

Aggression

Clonidine has been reported to be effective in open-label studies of aggressive children (Dawson et al., 1989; Comings et al., 1990; Kempf et al., 1993; Schvehla et al., 1994; Chandran, 1994). Doses of up to 0.4 mg/day of clonidine have been used so that reduction of aggression may also be due to sedation (Riddle et al., 1999). In an open trial of guanfacine (mean dose 3.2 mg/day) in 13 children with ADHD, Hunt et al. (1995) did not observe improvement in aggression. There have been no controlled studies assessing the efficacy of clonidine or guanfacine

in treating aggression. Such studies are clearly warranted because effective treatment of severely aggressive children is often highly problematic.

Sleep Problems

Sleep difficulties are not uncommon in children with ADHD. The sedating effects of clonidine (and, to a lesser extent, guanfacine) have resulted in their being used in ADHD patients with sleep disturbances. Reduced sleep latency was noted in 15 children with ADHD treated openly with clonidine 0.05–0.1 mg at bedtime who had sleep problems while being treated with methylphenidate (Rubinstein et al., 1994). Wilens et al. (1994) treated sleep problems in over 100 children with ADHD with open-label clonidine 0.05–0.4 mg at bedtime with initiation of sedative effects within 30 minutes that persisted until the morning. Clonidine was effective in ADHD patients with spontaneous (non-stimulant-associated) and stimulant-induced sleep disturbances. More recently, Prince et al. (1996) conducted a chart review and found that clonidine was effective in ameliorating sleep disturbances in 62 patients with ADHD. There have been no controlled studies of clonidine or guanfacine for sleep disorders. While clonidine may be an effective adjunct in ADHD patients who have spontaneous or stimulant-induced sleep problems, caution is indicated in view of rare but potentially serious side effects associated with methylphenidate-clonidine combinations (Cantwell et al., 1997). Guanfacine might be considered, although its sedative effect is typically less than clonidine's. We also do not recommend clonidine or guanfacine use for sleep disorders in children without ADHD.

Autism

Fankhauser et al. (1992) conducted a double-blind, placebo-controlled study of the transdermal clonidine patch in nine children with autistic disorder. Reduction in "hyperarousal" was reported by both parents and clinicians. In another double-blind study, the effectiveness of clonidine 0.15–0.20 mg/day was compared to placebo in eight children with autism (Jaselskis et al., 1992). No statistically significant differences were observed between clonidine and placebo. Teacher ratings of aberrant behavior and parent ratings of oppositional behavior were decreased, but interpretation of the results of this study was hindered by the fact that problematic side effects resulted in six of the eight patients being unable to tolerate long-term clonidine therapy. There have been no controlled studies of guanfacine in autistic patients. Since it may have fewer problematic side effects than clonidine, particularly sedation, study of guanfacine for this condition is merited.

Fragile X Syndrome

Hagerman et al. (1998) found that open-label use of clonidine alone or in combination with methylphenidate in 35 children with fragile X syndrome resulted in

decreased hyperactivity, irritability, and tantrums as perceived by the patients' parents. There were also fewer bedtime problems. There have been no controlled studies of clonidine or guanfacine for this condition. Such studies are clearly warranted.

Opioid Withdrawal

Clonidine has been successful in helping patients to withdraw from narcotics (Gold et al., 1978; Arana and Hyman, 1991) (see Chapter 19). It has been demonstrated to be more effective than morphine or placebo in decreasing the autonomic symptoms of opiate withdrawal, although not improving the subjective symptoms associated with withdrawal (Kaplan and Sadock, 1991). Clonidine can be used either alone or to facilitate the withdrawal from methadone, which is commonly employed in opiate detoxification protocols (Hoder et al., 1984; Jasinski et al., 1985; Charney et al., 1986). In adults, doses of 0.15 mg two times per day are used. The use of clonidine and guanfacine for this purpose has not been well studied in children and adolescents.

Nicotine Withdrawal

Although there had been some initial excitement regarding clonidine's facilitating the cessation of smoking in nicotine-dependent adults, Franks and colleagues (1989) performed a randomized, controlled trial of clonidine for smoking cessation and demonstrated it to be of no benefit. Therefore, clonidine and guanfacine cannot be recommended for facilitating cessation of smoking.

Bipolar Disorder in Adults

During the early 1980s some reports began to suggest a potential role for clonidine in the treatment of bipolar disorder (Jouvent et al., 1980; Hardy et al., 1983; Zubenko et al., 1984a). Patients were treated with clonidine 0.2–0.4 mg two times per day in combination with lithium and/or carbamazepine and improved 2–3 days after an effective dose of clonidine was reached. Kontaxakis and colleagues (1989) demonstrated that adults with bipolar disorder treated with antipsychotics and antidepressants experienced quick amelioration of symptoms without significant side effects when clonidine was added to the regimen. However, Giannini and colleagues (1986) conducted a double-blind crossover study of 24 patients with bipolar disorder in the midst of a manic episode and found lithium to be significantly more effective than clonidine. Clonidine's effectiveness in this disorder is far from clear, and several other alternative agents appear to be far more promising in the treatment of mania, such as valproic acid, carbamazepine, verapamil, lamotrigine, and nifedipine (Arana and Hyman, 1991). No published data on clonidine or guanfacine exist for children and adolescents with bipolar disorder. Given the existence of more promising medications, they cannot be recommended for the treatment of children and adolescents with bipolar disorder.

Psychosis

Reports of clonidine's effectiveness in decreasing psychosis and anxiety in psychotic patients have been published (van Kammen et al., 1989; Uhde et al., 1989). Van Kammen and colleagues (1989) conducted a double-blind study and showed that 4 of 13 drug-free, relapsed paranoid schizophrenic adult patients improved significantly on clonidine. There has been further suggestion that clonidine may also ameliorate tardive dyskinesic movements in these schizophrenic patients. Van Kammen and colleagues (1989) also found that an improvement in psychosis, anxiety, and negative symptoms correlated significantly with the response of growth hormone to a clonidine challenge test before treatment, suggesting that patients with "normal" CSF norepinephrine levels and normal or high α_2 activity might be more likely to respond to clonidine treatment. This lack of established efficacy makes it impossible to offer documented recommendations for its use in psychotic patients. There are no published data on the use of clonidine or guanfacine in psychotic children and adolescents. Because of their potential antidyskinetic properties and their ability to decrease hyperarousal, it would be valuable to conduct a controlled study using clonidine or guanfacine, either alone or as an adjunct in the treatment of psychotic children and adolescents. It would be interesting to determine whether guanfacine has a favorable impact on attention in psychotic children and adolescents as the disturbances in attention are often present in psychotic states.

Anxiety and Panic Disorders

In general, clonidine has not been demonstrated to produce long-term benefit in adults with anxiety or panic disorders (Hunt et al., 1988, 1990), although it may temporarily decrease the intensity of an acute anxiety attack. Uhde and colleagues (1989) showed that when oral clonidine was given chronically to 18 patients with panic disorder on a double-blind, flexible-dose schedule for 10 weeks, some patients reported improvement in anxiety symptoms, but this improvement was not reported by the group as a whole. Clonidine was also shown to produce a significant, acute reduction in the anxiety of 12 panic disorder patients as compared to 10 controls when 2 $\mu\text{g}/\text{kg}$ IV clonidine and placebo were administered (Hunt et al., 1988, 1990).

Clonidine 0.15–0.7 mg/day was shown to quicken the tapering of alprazolam in panic disorder adult patients (Fyer et al., 1988). Although during the acute withdrawal period there was no relapse of panic symptoms, clonidine treatment did not prevent the subsequent recurrence of such symptoms. Moreover, Goodman and colleagues (1986) reported the ineffectiveness of clonidine in the treatment of the benzodiazepine withdrawal syndrome in three patients. It seems doubtful that clonidine or guanfacine will prove to be a significantly beneficial treatment for anxiety disorders. There are no data on children and adolescents.

Neuroleptic-Induced Akathisia

Clonidine doses of 0.15–2.0 mg/day have been reported to improve the subjective and objective signs and symptoms of akathisia (Zubenko et al., 1984b; Adler et al., 1987; Arana and Hyman, 1991). This treatment has been limited because of clonidine's hypotensive side effects, which can be particularly troublesome when lower-potency neuroleptics (which can have significant hypotensive side effects of their own) are used at the same time. Further study is clearly warranted. Clonidine or guanfacine should be utilized only after all other treatment options have been explored, including neuroleptic dosage reduction, anticholinergic medications, beta-blockers, and benzodiazepines (Arana and Hyman, 1991). There are no data on children and adolescents. Because of its significant side effect profile, we do not recommend that clonidine be used to treat akathisia. Guanfacine may have fewer side effects but cannot be recommended for use at this time.

Posttraumatic Stress Disorder

Friedman (1988) showed that in adults with PTSD, clonidine reduced anxiety, hyperarousal, and intense and intrusive flashbacks of the precipitating trauma but did not ameliorate avoidant-type behaviors. Kinzie and Leung (1989) treated 68 Cambodian refugees diagnosed with chronic PTSD and depression with clonidine and imipramine, which helped reduce depressive symptoms, anxiety, sleep disturbances, and nightmares. There are no data for clonidine or guanfacine in children or adolescents.

Social Anxiety Disorder (Social Phobia)

Clonidine has enjoyed some modest success in the treatment of social phobias (Friedman, 1988). Further study is needed before recommendations regarding the use of clonidine or guanfacine for this disorder can be made. There are no data on children and adolescents.

Borderline Personality Disorder

In view of the intense hyperarousal states that are frequently seen in patients with borderline personality disorder, clonidine may prove useful in its treatment (Hunt et al., 1988, 1990). There are no data on children and adolescents.

Contraindications

See Table 3 for contraindications to clonidine and guanfacine use.

Depression

Clonidine should be avoided for children and adolescents who have significant depressive symptoms and/or family history of mood disorders (Hunt et al., 1990). Clonidine and other α_2 agonists, such as α -methyldopa, have been reported to

TABLE 3 Contraindications to Clonidine and Guanfacine Use

Absolute:
None
Relative:
Depression in patient or family history (clonidine > guanfacine)
Cardiovascular disorders (clonidine > guanfacine)
Renal disease (guanfacine > clonidine)
Liver disease (clonidine > guanfacine)
Skin disease/irritation (for clonidine skin patch only)

have significant depressive side effects (Physicians' Desk Reference, 2001) (see "Side Effects"). Guanfacine may pose less risk for causing depressive side effects, although further study is necessary.

Cardiovascular Disorders

Clonidine and guanfacine's only FDA-established indication is for hypertension, and they should, in general, be avoided for patients with cardiovascular disease because of their hypotensive side effects (Hunt et al., 1988, 1990). When their use is necessary, careful monitoring is required. This monitoring should consist of the taking of orthostatic blood pressure and pulse measurements prior to each dose when initiating clonidine and guanfacine and at each dose increment until a stable dose is achieved. A baseline ECG, and subsequent ECGs if any clinical symptoms and/or significant blood pressure or pulse changes are noted, should be performed. Cardiology consultation is also indicated. The inpatient setting is the safest place for such a medication trial to be implemented. If this is not possible, frequent office monitoring is indicated. If the patient's family has access to a blood pressure cuff, family members can be taught to take these blood pressure and pulse measurements and asked to notify their physician if there is any anomaly.

While clonidine is not contraindicated in patients on methylphenidate, methylphenidate-clonidine combination therapy has received significant attention recently because of rare but potentially serious cardiotoxic interactions (see "Side Effects"). We recommend use of guanfacine-methylphenidate combination therapy before initiating clonidine-methylphenidate combination therapy.

Renal Disease

Since clonidine (65%) and guanfacine are metabolized by the kidney, they are relatively contraindicated for children and adolescents with kidney disease (Hunt et al., 1990).

Allergic Reaction

As with any medication, a history of an allergic reaction to clonidine or guanfacine should preclude their use. However, an allergic reaction or other side effect to clonidine does not necessarily mean that the same reaction will occur with guanfacine or vice versa. Patients and their parents should be informed that a similar reaction may occur but that in many cases this does not occur. Similarly, lack of response to clonidine does not mean that a patient will fail to respond to guanfacine or vice versa.

Pregnancy

There is virtually no psychiatric indication for clonidine or guanfacine use during pregnancy.

Skin Irritation/Disease—Clonidine Skin Patch Only

Children and adolescents with significant problems with skin irritation and dermatological conditions may not be candidates for the skin patch (Hunt et al., 1990). If the patient is a known responder to clonidine but refuses to take oral medication, as at school, and the teachers and parents are unable to enforce its ingestion, dermatological consultation may be helpful. In general, however, the clonidine skin patch should be avoided in these patients.

Liver Disease

Clonidine is relatively contraindicated for children and adolescents with liver disease as it is, in part (35%), metabolized by the liver. Guanfacine may be a safer alternative in patients with liver disease, although careful monitoring is indicated and this should only be done in consultation with the physician specialist treating the hepatic illness.

Side Effects

Guanfacine appears to have fewer overall side effects than clonidine (Table 4) (Riddle et al., 1999). A recent chart review conducted on 85 patients with mean age of 10 years treated with guanfacine found it to be well tolerated (Horrigan and Barnhill, 2000). Although 35 patients (41%) were noted to have one or more side effects, most were self-limited and did not result in medication discontinuation.

Sedation

The most common side effect that children and adolescents experience while on clonidine is sedation, with complaints of lethargy and sluggishness (Hunt et al., 1988, 1990). This is often manifest as daytime sleepiness and may be particularly problematic in school (Hunt, 1987). It is important to realize that many of the

TABLE 4 Side Effects of Clonidine and Guanfacine^a

Common:
Sedation
Hypotension
Headache/dizziness
Gastrointestinal
Irritability
Uncommon:
Depression
Cardiovascular/cardiac arrhythmia
Rebound hypertension
Retinal degeneration
Skin irritation with skin patch
Anticholinergic
Vivid dreams/nightmares/disrupted sleep
Appetite increase or decrease
Sexual dysfunction
Fluid retention
Anxiety
Increase blood glucose
Raynaud's phenomenon

^a Guanfacine treatment is typically associated with fewer side effects than clonidine treatment.

children receiving clonidine for ADHD, Tourette's disorder, and other disruptive behavior disorders have extremely high baseline hyperarousal rates, so that sedation may be missed in this population because the parents and teachers may be so relieved that the child is not acting out. Similarly, children with high levels of baseline disruptive behavior may impress observers as being relatively sedated, when, in fact, their more "normal," less hyperactive behavior is such a marked change that it seems as though the child must be sedated.

Sedation is most noticeable and problematic during the first month of treatment (Hunt et al., 1988, 1990). Fortunately, it usually remits progressively thereafter. In some children on clonidine, however, the sedation persists, an effect that may be more pronounced in those with lower baseline levels of arousal (Hunt et al., 1988, 1990). Dose adjustment is not always successful in decreasing sedation, which often interferes with the patient's activities of daily living, and the medication must, therefore, be discontinued.

Guanfacine treatment is associated with a lower risk for sedation than clonidine (Riddle et al., 1999). Scahill and colleagues (2000) studied guanfacine treat-

ment of 34 medication-free patients with ADHD and tic disorders. Only one patient experienced problematic sedation requiring withdrawal at 4 weeks of treatment.

Hypotension

Children frequently experience a 10% decrease in systolic blood pressure when treated with clonidine, but this rarely results in clinical symptoms and is rarely significant (Hunt et al., 1988, 1990). Orthostasis occurs in less than 5% of children on clonidine (Hunt et al., 1988, 1990). Sedation appears to correlate with decreased blood pressure. Hypotension is less common with guanfacine treatment, with recent investigation demonstrating no significant impact on vital sign measurement (Horrigan and Barnhill, 2000). This may be due, in part, to the fact that guanfacine is less sedating than clonidine.

Cardiovascular Disease

Clonidine acutely decreases cardiac output by 10–20%, but during long-term treatment the cardiac output returns to baseline (Hunt et al., 1988, 1990). Clonidine does not alter renal blood flow or GFR, but it does lower peripheral resistance and pulse. However, this is rarely clinically significant in physically healthy children and adolescents.

Chandran (1994) and Dawson et al. (1989) have reported cardiac side effects including decreased heart rate, first-degree heart block, arrhythmias, non-conducted P waves, supraventricular premature complexes, nonspecific intraventricular conduction delay, T-wave abnormalities, and anterior ischemia. However, in these reports clonidine was being administered with other medications, which makes delineating clonidine's role in these adverse events more complicated. Swanson et al. (1995) reviewed 23 Med Watch reports of side effects in children treated with clonidine, which included four reports of sudden cardiac death in patients treated with clonidine-methylphenidate combination therapy. The relative risk for sudden death with methylphenidate-clonidine combination therapy was 25:1 as compared to treatment with clonidine or methylphenidate monodrug therapy. It should be noted that these cases of sudden cardiac death in patients treated with methylphenidate-clonidine combination therapy were complicated by potentially confounding factors including preexisting cardiac abnormalities and patients being treated with other medications in addition to methylphenidate and clonidine (Fenichel, 1995; Popper, 1995). Swanson et al. (1995) proposed two pharmacodynamic mechanisms by which methylphenidate-clonidine combination therapy may trigger cardiotoxic reactions: (1) peak clonidine sedative-hypotensive-bradycardia effects coinciding when the effects of methylphenidate are decreasing and (2) peak effects of methylphenidate with its potentiation of activation-hypertension-tachycardia coinciding when the peak effects of clonidine are waning. Cantwell et al. (1997) proposed that these opposing mechanisms

of interactions could result in cardiotoxicity leading to sudden cardiac death. As pointed out (see “Contraindications”), caution should be employed when utilizing this medication for patients with underlying cardiovascular disease. While guanfacine may pose less risk for cardiovascular side effects (Horrigan and Barnhill, 2000), further study is necessary and close monitoring and consultation with a cardiologist is advised if guanfacine treatment is considered in a child or adolescent with underlying cardiovascular disease.

Headache and Dizziness

Headache and postural dizziness are seen most commonly during the first month of treatment and are most often short-term side effects that dissipate after the first month (Hunt et al., 1988, 1990). They seem to appear most commonly when the dose is rapidly increased.

Stomachache/Nausea/Vomiting

Gastrointestinal upset most commonly occurs at the very beginning of treatment and usually remits (Hunt et al., 1988, 1990).

Depression

The α_2 -adrenergic agonists have been strongly associated with depressive side effects (Physicians’ Desk Reference, 2001). In fact, some clinicians now try to avoid these agents when treating hypertension in favor of other equally (or more) effective antihypertensive agents without α_2 activity. It is important to note that although clonidine can cause depression in children and adolescents, most have significant depressive symptoms at the start of clonidine treatment as well as a personal or family history of mood disorders (Hunt et al., 1988, 1990).

Irritability

Irritability is a common side effect of clonidine and is often confused with the symptoms of the psychiatric disorder it is being used to treat, e.g., ADHD. Leckman et al. (1991) noted that approximately 70% of patients on clonidine reported irritability. Irritability appears to be seen much less commonly in patients treated with guanfacine.

Rebound Hypertension

Caution is required when the patient is taking a beta-blocker, since a clonidine or guanfacine–beta-blocker combination can result in clinically significant rebound hypertension (Hunt et al., 1988, 1990). In addition, when clonidine and guanfacine have been administered chronically and/or at high dosages, abrupt withdrawal may result in a dangerous rebound hypertension. This adverse effect is well documented with clonidine (Lekckman et al., 1986). The risk of rebound hypertension is lower with guanfacine (Wilson et al., 1986). This hypertension is usually tran-

sient, but unless properly treated it can jeopardize the child's safety. It is best never to withdraw clonidine or guanfacine abruptly, but to taper these medications prior to discontinuing them (see "Dosage and Administration"). When clonidine is abruptly withdrawn, other signs and symptoms, in addition to rebound hypertension, include anxiety, chest pain, increased and/or irregular pulse, headache, GI upset, sleeping problems, and tremor (Hunt et al., 1990).

Retinal Degeneration

A total of 353 adults treated with clonidine for 20 or more years showed no evidence of retinal degeneration (Hunt et al., 1988, 1990). There are no data for clonidine and guanfacine in children, but this appears to be an unlikely risk.

Skin Irritation—Clonidine Skin Patch Only

It has been shown that the use of the transdermal clonidine skin patch can result in localized contact dermatitis with itching and erythema in nearly 40% of children (Hunt et al., 1988, 1990). Even though the Band-Aid that can be placed over the patch may help keep the patch on, the Band-Aid appears to increase the frequency and symptoms of the contact dermatitis. This dermatitis often develops within the first 3 weeks of the patch's use and may mandate its discontinuation. Hunt and colleagues (1988) did find, however, that in contrast to adults who have been reported to be at increased risk for developing a generalized skin rash when they are switched from the patch to oral clonidine, this did not result in 50 children who were placed on oral clonidine after failing the patch.

Anticholinergic Effects

Approximately 50% of adult patients on clonidine report anticholinergic side effects such as dry mouth, especially during the first month of treatment (Arana and Hyman, 1991). Children, however, appear to be far less sensitive to these side effects (Hunt et al., 1988, 1990).

Vivid Dreams/Nightmares/Disrupted Sleep

Symptoms of sleep disturbance are not uncommonly seen in children and adolescents with underlying psychopathology, so differentiating the medication's side effect from the patient's disorder can be difficult. Approximately 10% of adults complain of sleep disturbances while taking clonidine (Hunt et al., 1988, 1990). This has not been well described in children and adolescents and requires further study.

Appetite Increase or Decrease

Clonidine has been reported to increase or decrease both appetite and weight (Hunt et al., 1988, 1990). A weight gain of more than 5 pounds is, however, quite unusual. When it does take place, it tends to be observed in children with

ADHD who had lost weight on methylphenidate and subsequently experienced a weight rebound on clonidine (Hunt et al., 1988, 1990).

Sexual Dysfunction

As with many psychotropic and antihypertensive drugs, clonidine and guanfacine have been reported to result in decreased libido, impotence, or decreased sexual activity in adults receiving these medications (Physicians' Desk Reference, 2001). This has not been well described in adolescents and requires further study.

Fluid Retention

Fluid retention has been reported to occur, but it can be corrected with diuretic therapy (Hunt et al., 1988, 1990; Arana and Hyman, 1991).

Anxiety

Anxiety and nervousness have been reported as occasional side effects of clonidine treatment (Physicians' Desk Reference, 2001).

Increase in Blood Glucose

Increased blood glucose is rarely significant, and usually only for diabetic patients (Hunt et al., 1988, 1990).

Raynaud's Phenomenon

This syndrome, characterized by feelings of cold and pain in the fingers and toes, is a rarely observed side effect when clonidine is used (Physicians' Desk Reference, 2001).

Important Considerations When Prescribing Clonidine or Guanfacine

See Table 5 for precautions when using these agents.

Overdose

Overdose with clonidine or guanfacine can be a life-threatening medical emergency. Characteristic symptoms of overdose include decreased or absent reflexes, lethargy or somnolence, dilated pupils, hypotension and bradycardia, hypoventilation, and irritability (Physicians' Desk Reference, 2001). Large overdoses may also present with seizures, apnea, reversible cardiac conduction defects, and arrhythmias. The treatment of clonidine or guanfacine overdose includes removing all clonidine or guanfacine systems, such as the clonidine skin patch. The use of IV fluids and/or pressors to treat hypotension, treatment with atropine for bradycardia, and careful monitoring of the patient's respiratory status are fre-

TABLE 5 Important Considerations When Prescribing Clonidine or Guanfacine

Use with caution in children and adolescents with:
Hypertension
Cardiovascular disease
Cerebrovascular disease
Diabetes
Depression
Beta-blockade (i.e., on propranolol)

quently required interventions after a clonidine overdose (Arana and Hyman, 1991; Physicians' Desk Reference, 2001).

Abuse

There is virtually no risk for the recreational abuse of clonidine or guanfacine (Lowenthal et al., 1988).

Drug Interactions

See Table 6 for clonidine and guanfacine interactions.

Available Preparations and Cost

See Table 7 for commercially available clonidine and guanfacine preparations.

Initiating and Maintaining Treatment

The practicing clinician who decides to start clonidine or guanfacine must ensure that a comprehensive baseline history is taken and that the child or adolescent receives a physical examination. Blood pressure and pulse measurements should be documented. The clinician should also strongly consider obtaining a baseline CBC and differential, electrolytes, BUN and creatine, thyroid function tests, LFTs, an ECG, and fasting blood glucose (Hunt et al., 1988, 1990).

While the child or adolescent is on clonidine or guanfacine, blood pressure and pulse measurements should be obtained each week until the dose is stabilized. After the dose is stabilized, blood pressure and pulse should be monitored every 2 months (Hunt et al., 1988, 1990). More frequent monitoring can be considered if sedation and/or other side effects are noted.

It is important to emphasize to the patient and family the potentially severe consequences that may result from the abrupt discontinuation of clonidine or guanfacine. Therefore, when prescribing clonidine or guanfacine it is important

TABLE 6 Clonidine and Guanfacine Interactions

Increase drug effect of:

- Heterocyclic antidepressants
- Antipsychotics
- Anticholinergic medications
- CNS depressants (e.g., alcohol)

Decrease drug effect of:

- Beta-blockers

Increase effects of clonidine and guanfacine:

- Diuretics
- Other antihypertensive medications
- CNS depressants

Decrease effects of clonidine and guanfacine:

- Heterocyclic antidepressants
- Sympathomimetic drugs
- Nonsteroidal anti-inflammatory analgesics

Increases:

- Growth hormone levels (short-term)
- Blood glucose

Decreases:

- Urinary catecholamines

May cause:

- Abnormal liver function tests
- Wenckebach periods of ventricular trigeminy

Source: Adapted from Lowenthal et al., 1988.

TABLE 7 Commercially Available Preparations of Clonidine and Guanfacine

Drug	Dosage forms	Average cost/day
Generic clonidine	0.1 mg	\$0.03
	0.2 mg	\$0.04
	0.3 mg	\$0.06
Catapres transdermal (skin patch)	TTS-1	\$1.18
	TTS-2	\$1.99
	TTS-3	\$2.75
Guanfacine	1 mg	\$1.20
	2 mg	\$1.47

to ensure that proper follow-up takes place and that the family does not let the prescriptions run out, use clonidine or guanfacine on a p.r.n. basis, or alter the medication regimen without physician consultation.

The parent and child should also be advised that long-term treatment may be required. Hunt and colleagues (1988) reported on children treated with clonidine for as long as 5 years with continued beneficial effect and without significant dose alteration.

Clinical Practice

Dosage and Administration of Oral Clonidine

Tourette's Disorder. To reduce daytime sleepiness and lethargy, clonidine is usually first initiated at bedtime (Hunt et al., 1988, 1990). The recommended starting dose is 0.05 mg at bedtime (half of the smallest available tablet of 0.1 mg) (Table 8). The dose should be increased gradually by 0.05 mg every 3–7 days to facilitate the child's adjustment to the medication. Even with this gradual increase in dosing, sedation is still usually the limiting factor in dose elevation (Hunt et al., 1988, 1990; Bruun, 1983). Sedative effects have been found to peak $1/2$ – $1\frac{1}{2}$ hours after a dose of clonidine has been administered. Oral clonidine is best given in small divided doses, that is, three to four times per day with meals and at bedtime. Bruun (1983) has noted that some patients experience a decrease in beneficial effects approximately 5 hours after the last dose, further arguing for the total daily dose to be administered in three to four divided doses. The treatment of Tourette's disorder usually requires 3–4 $\mu\text{g}/\text{kg}/\text{day}$ (Hunt et al., 1988, 1990). Dosages above this level may be required but commonly produce unacceptable side effects, such as sedation and lethargy.

TABLE 8 Clinician's Guide to Using Clonidine for Tourette's Disorder and ADHD in Children and Adolescents

Tourette's disorder	ADHD
Start with 0.05 mg, increase by 0.05 mg every 3–7 days	Start with 0.05 mg, increase by 0.05 mg every 3–7 days
Optimal dose 3–4 $\mu\text{g}/\text{kg}/\text{day}$, three to four times a day	Optimal dose 3–6 $\mu\text{g}/\text{kg}/\text{day}$
After stable oral dose is achieved, may switch to skin patch (same dose)	After stable oral dose, may switch to skin patch
Not FDA approved	Not FDA approved

It should be noted that many psychiatrists have been taught to start clonidine or guanfacine with a morning dose and to add doses during the day as needed. This is fairly common in clinical practice as well as in clinical trials. A benefit of this approach is that the sedative side effects may be cumulative across doses. Only by adding doses sequentially (e.g., starting with a morning dose) can the clinician determine how to set the interval between doses. If they are too close, there is a risk for cumulative sedation with later doses, while if the doses are given too far apart, rebound/withdrawal may occur. There is an urgent need for further controlled study for delineation of optimal dosing of clonidine and guanfacine.

The patient and family should also be informed that during the initial treatment phase, the Tourette's symptoms, including motor and phonic tics, may actually worsen (Hunt et al., 1988, 1990). Huk (1989) has described how this transient exacerbation of tics in the treatment of Tourette's disorder with clonidine often dissipates once a stable dose has been achieved, usually 2–4 weeks after treatment has begun. A dose adjustment—a decrease, and possible reincrease after tolerance to clonidine's side effects has resulted—is often necessary.

Cohen and colleagues (1980) have developed a very useful paradigm in which they describe five phases commonly experienced by patients on clonidine for Tourette's disorder. In the first phase the patient often experiences decreased subjective distress, agitation, and anger and, therefore, feels more tranquil and less aroused. The second phase begins approximately one month after clonidine has been started. During this phase, further behavior control is achieved, vocal and motor tics dissipate, and obsessive and compulsive behaviors also decrease. This usually corresponds to therapeutic dosages, 3–4 $\mu\text{g}/\text{kg}/\text{day}$. Phase 3 occurs approximately 3 months after treatment, when continued improvement is observed. Phase 4 is experienced by some (but not all) patients 5 or more months after clonidine was started. They may require further increases in their clonidine doses to prevent a relapse. Unfortunately, doses this high are often associated with intolerable side effects. Adjunctive therapy with clonazepam (Steingard et al., 1994) or, if this is unsuccessful, neuroleptics, particularly the atypical neuroleptics, might be considered, since their combined use sometimes allows lower dosages of clonidine to be used. These other medications have their own sedating side effects, however. Finally, phase 5 is characterized by further tolerance to clonidine, generally at dosages that cannot be increased further.

Tourette's disorder may require long-term treatment with clonidine (Hunt et al., 1988, 1990). It is very important that those children and adolescents who have been on chronic therapy be gradually tapered off clonidine to avoid rebound hypertension.

We wish to underscore that we do not recommend routine use of clonidine for Tourette's disorder. We recommend that guanfacine be used prior to using

clonidine for this condition. Guanfacine also has a more favorable side effect profile than clonidine.

ADHD. The treatment of ADHD with clonidine (Table 8) usually requires dosages of 3–4 $\mu\text{g}/\text{kg}/\text{day}$ (Hunt et al., 1988, 1990). It is almost never necessary to exceed doses of 8 $\mu\text{g}/\text{kg}/\text{day}$. Intolerable side effects frequently make it impossible to attain such high doses. Children and adolescents with particularly high hyperarousal, agitation, and aggression baselines with poor frustration tolerance may be best able to tolerate high-dose clonidine. Dosage and administration should follow that described for Tourette's disorder. Divided doses given three to four times per day are preferred. Maximum doses may be higher than those required for Tourette's disorder, particularly for those children with high levels of hyperarousal. As with Tourette's disorder, sedation and other side effects are not uncommon and frequently mandate clonidine's adjustment, sometimes even resulting in its discontinuation. For those who do respond, long-term treatment is often required. Clonidine may not exert its effect until 2–3 months after its initiation, and, therefore, no patient should be considered a treatment failure until this length of time has elapsed.

Clonidine should not be prescribed for ADD without hyperactivity. We recommend a trial of guanfacine before clonidine for both ADD without hyperactivity as well as for ADHD because it may be effective in reducing both hyperactivity and attention disturbances as well as its more favorable side effect profile.

Management of Specific Side Effects of Oral Clonidine

Sedation

When sedation occurs during the first month of treatment, decreasing the rapidity with which the dose is increased may prove helpful (Hunt et al., 1988, 1990). The dose can be increased by 0.05 mg increments every 10–14 days instead of on a weekly basis. For smaller children, it might be advisable to increase the dose by 0.25 mg per week (one-fourth of a 0.1 mg tablet). Sometimes, it may even be necessary to decrease the clonidine dose temporarily until the patient is capable of tolerating the lower dose. When this has been successfully achieved, a subsequent gradual increase of the dose may be initiated. Combination therapy often allows lower overall clonidine dosage, as when used in conjunction with methylphenidate to treat ADHD. Finally, sometimes the sedation and lethargy can be ameliorated by switching from oral clonidine to the skin patch, which produces a smaller dose pulse (Hunt et al., 1988, 1990).

Gastrointestinal Upset

Although GI upset is usually transient, it can be disconcerting; gradual dose increments and ingestion after meals may help ameliorate this side effect (Hunt et al., 1988, 1990).

Hypotension

Hypotension may occur in conjunction with sedation. If the systolic and/or diastolic blood pressure decreases by more than 10 mmHg, decreasing the dose is indicated (Hunt et al., 1988, 1990). If this is unsuccessful, switching from oral clonidine to the skin patch might reverse the blood pressure change. Performing an ECG and getting a cardiology consultation may be indicated.

Depression

Depression has been found to occur most commonly in children who have had prior depressive episodes, current depressive symptoms, and/or family history of mood disorders (Hunt et al., 1988, 1990). When clinical judgment deems clonidine treatment necessary, or in patients who develop a depressive episode *de novo*, decreasing the dose or switching to the skin patch may be effective in reducing the depressive symptoms (Hunt et al., 1988, 1990).

Dosage and Administration—Transdermal Therapeutic System

The clonidine skin patch is available only in proprietary form—Catapres-TTS 1, 2, and 3—which correspond to oral clonidine doses of 0.1, 0.2, and 0.3 mg. While these are the only doses of the skin patch available, cutting the patch can produce intermediate doses so that oral doses can be achieved with the skin patch (Hunt et al., 1988, 1990).

It is generally not advisable to start clonidine treatment with the skin patch (Hunt et al., 1990) because oral clonidine can be used more easily to determine treatment response, making the switch to an equivalent dose of transdermal clonidine easier. Absorption via the skin patch is believed to be more variable than that after the oral administration of clonidine. It is important to emphasize that there is no fixed ratio of doses between routes of administration, and because of the significant variability between the two treatment approaches, modification and adjustment are frequently required when switching from one to the other (Hunt et al., 1988, 1990).

When selecting the site for administration of the clonidine patch in children and adolescents, it is important to choose an inaccessible area without hair on the lower back (Hunt et al., 1990). Children with ADHD and those who are just normally active might inadvertently (or intentionally) remove the patch and either lose it or put it back on. In either case, the dosing regimen is affected, and accurate assessment of its efficacy versus toxicity is made considerably more difficult. The skin should be prepared by washing with soap and water and then drying. The 1.0 × 1.5 cm patch should be attached to the designated area like a Band-Aid. To make certain that the skin patch stays on the back, a protective 3 cm white adhesive strip may be applied over the patch. The problem with this is that

the adhesive can exacerbate and increase the risk of developing skin irritation from the clonidine skin patch (see below).

One frequent concern of parents relates to what they should do when their child exposes the patch to water, as when swimming (Hunt et al., 1990). The clonidine skin patch is believed to be resilient to brief water exposure and does not have to be replaced after a shower or a bath (Hunt et al., 1988, 1990), but parents should be warned that the patch may require replacement during particularly humid summer days or when the child is exposed to water for extended periods, such as when swimming all day. This is not absolute, and the parents should be aware that they will have to monitor their child and assess the efficacy of the patch after long exposure to water.

The patch is believed to be effective for 5 days (Hunt et al., 1990) and should be replaced after this time. Many parents and children prefer this method of receiving medications, since it does not require pill taking and minimizes the risk of forgetting a dose of medication.

Nonspecific sedation may be noted soon after the skin patch is initiated. Clinical response is rarely observed before 2 weeks of treatment with clonidine (Hunt et al., 1988, 1990) and usually takes a month before a significant clinical response occurs. It can take up to 3 months for the maximal therapeutic effect to occur, and a medication trial may necessitate 2 months of treatment before a child is considered to have failed the clonidine trial. Usually, after the primary response of decreasing hyperarousal, improvements in learning and attention span, compliance, social skills, irritability, and mood may occur (Hunt et al., 1988, 1990).

Management of Specific Side Effects of the Skin Patch

Skin Irritation

Hydrocortisone cream 1% can help ameliorate the skin irritation by decreasing erythema and itching (Hunt et al., 1990). In addition, not using the optional protective adhesive patch cover may reduce the skin irritation (Hunt et al., 1988, 1990). Consultation with a dermatologist may also be advisable. In some cases, however, it is necessary to return to oral clonidine. Fortunately, in contrast to adults, who not uncommonly are predisposed to adverse generalized skin reactions when switched back to oral clonidine, this does not appear to happen in children and adolescents (Hunt et al., 1988, 1990).

Dosage and Administration of Guanfacine

The principles of dosage and administration of guanfacine (Table 9) and management of specific side effects are similar to those mentioned above for clonidine. Because of its more favorable side effect profile and its hypothesized selective effect on attention (Arnsten et al., 1996), we recommend its use before clonidine

TABLE 9 Clinician's Guide to Using Guanfacine for Tourette's Disorder and ADHD in Children and Adolescents

Tourette's disorder	ADHD
Start with 0.5 mg, increase by 0.5 mg every 3–7 seven days	Start with 0.5 mg increase by 0.5 mg every 3–7 days
Optimal dose 3.5 mg/day administered three to four times per day	Optimal dose 3.5 mg/day administered three to four times per day
Not FDA approved	For severe, refractory cases may need to increase dose gradually by 0.5 mg increments every 3–7 days to maximum daily doses of 6–7 mg/day; careful monitoring for cardiac and other side effects is indicated
	Not FDA approved

for ADHD, ADD without hyperactivity, and tic disorders with and without comorbid ADHD. Typical dose ranges of 1.5–4 mg/day appear to be most effective in ameliorating ADHD and tic symptoms. The recommended dosing strategy is to start guanfacine at 0.5 mg (one-half pill) and then increase the dose by 0.5 mg (one-half pill) increments every 3–7 days to a maximum of 4 mg/day. A dose of 2.5 mg/day is a likely dose capable of achieving maximal efficacy with minimal toxicity. This dosage is given in divided doses of 0.5 mg at breakfast, 0.5 mg at lunch, 0.5 mg at 4 p.m., and 1 mg at bedtime. Alternative dosing strategies that have been effective with minimal side effects include 0.5 mg b.i.d. and 1 mg in the evening or 1, 0.5, and 1 mg (Scahill et al., 2000). Although not supported by published data, in some patients with particularly severe hyperactivity, daily divided doses of 6–7 mg/day may be needed to achieve beneficial effects (McDougle, personal communication). Others (Scahill, personal communication) have not observed additional benefit of guanfacine at doses greater than 4.5 mg/day.

How to Withdraw Clonidine and Guanfacine

It is essential that clonidine and guanfacine be withdrawn gradually. In children, if clonidine has been given for less than one week, abrupt discontinuation of the 0.05 mg bedtime dose does not usually result in rebound hypertension or other problems (Hunt et al., 1988, 1990). Similarly, if guanfacine has been given for less than one week, abrupt discontinuation of the 0.5 mg dose does not usually result in rebound hypertension or other problems. When clonidine has been dispensed for between 2 and 3 weeks, gradual tapering by 0.05 mg/day is required.

When guanfacine has been dispensed between 2 and 3 weeks, gradual tapering by 0.5 mg/day is required. After the child or adolescent has been on clonidine or guanfacine for one month or longer, an even more gradual tapering schedule is advised. In these patients, clonidine should be reduced by 0.05 mg every 3–5 days, while guanfacine should be reduced by 0.5 mg every 7 days. The more chronic the use, the more crucial it is that the clonidine or guanfacine taper be gradual.

Leckman and colleagues (1986) evaluated the behavioral, cardiovascular, and neurochemical impact of abrupt clonidine discontinuation in seven pediatric patients with Tourette's syndrome 9–13 years of age who had been treated with clonidine 3–8 µg/kg/day for 3 months. Marked worsening in tics was observed in five of the seven patients. Increased blood pressure, pulse, and motor restlessness were noted during the 3 days after clonidine was abruptly discontinued. During the withdrawal period, plasma levels of free 3-methoxy-4-hydroxyphenylglycol and homovanillic acid and urinary excretion of epinephrine and norepinephrine increased. It should also be noted that when clonidine was restarted after the 3-day withdrawal period, it took patients between 2 and 16 weeks for tics to decrease to levels observed prior to clonidine withdrawal (Leckman et al., 1986).

Similarly to children on stimulants who have periodic drug holidays (see Chapter 7), some children on clonidine or guanfacine can be maintained at doses of one-half to two-thirds the usual dose (Hunt et al., 1988, 1990). This should also be done gradually, as just described, to make sure that the child does not have rebound effects. Thus, it is probably not advisable to halve the dose over the Christmas recess, which is far shorter than a summer vacation. In contrast to stimulants with their lack of sequelae from abrupt discontinuation and their short half-lives, clonidine and guanfacine, with their potentially dangerous side effects from abrupt withdrawal and their longer half-lives, must always be gradually tapered, particularly when used over a long period. One final caution is that if a child or adolescent is on both clonidine or guanfacine and a beta-blocker, the beta-blocker should be discontinued several days before initiating the clonidine or guanfacine taper in order to avoid rebound hypertension (Hunt et al., 1988, 1990).

BETA-BLOCKERS

The beta-adrenergic blocking agents competitively antagonize epinephrine and norepinephrine actions at the beta-adrenergic receptors. These agents have many established indications for various cardiovascular disorders but currently have no FDA-established indications for use in psychiatric disorders. Nonetheless, there continues to be great interest in, and hope for, the potential efficacy of these agents in the treatment of certain psychiatric disorders.

Although controlled studies of beta-blockers in children and adolescents with neuropsychiatric disorders have not been performed, these medications continue to be prescribed to treat severe aggression and specific types of anxiety (particularly performance anxiety). Beta-blockers in children have been studied in children and adolescents with migraine and neurally-mediated syncope where they have been found to be safe and efficacious (Forsythe et al., 1984; Scott et al., 1995). For neuropsychiatric disorders, propranolol, a nonselective beta-1 and beta-2 antagonist, has thus far been the most investigated agent of its class and will be the focus of discussion in this chapter.

There is some evidence suggesting that propranolol is efficacious for aggressive patients with brain damage (Yudofsky et al., 1981; Ratey et al., 1983; Greendyke et al., 1984; Arnold and Aman, 1991). It has also been reported to be effective in the treatment of PTSD, anxiety and panic disorders, performance anxiety, and akathisia (Granville-Grossman, 1974; Kathol et al., 1980; Lipinsky et al., 1984; Famularo et al., 1988). Thus far it appears that propranolol's ability to decrease anxiety and agitation in certain psychiatric conditions is due more to its peripheral actions of slowing the increased heart rate characteristically associated with anxiety and hyperarousal states than to its central effects on noradrenergic beta receptors. The total number of patients entered into controlled studies is still far too small to declare a definitive outcome. At present, some clinicians use propranolol to treat children and adolescents with impulsivity and aggression, especially when there is CNS damage such as mental retardation or when they have failed first-line treatments of disruptive behavior disorders (Coffey, 1990). Because the efficacy and safety of propranolol has not been established in children and adolescents with psychiatric disorders, it is not possible to give documented recommendations regarding its use in this population. The few studies done involving this age group were not controlled and had very small sample sizes. In some cases, the beta-blocker was simply added to another psychoactive agent. Controlled studies comparing propranolol and placebo are necessary to determine its true role in the treatment of psychiatric disorders.

Buitelaar et al. (1996) compared pindolol and methylphenidate in 52 children with ADHD 7–13 years of age in a double-blind, placebo-controlled study. Pindolol 20 mg b.i.d. or methylphenidate 10 mg b.i.d. were prescribed for 4 weeks. While pindolol was comparably effective to methylphenidate in decreasing hyperactivity at home and in school and conduct problems at home, pindolol was less beneficial than methylphenidate during psychological testing and for conduct problems in school. Moreover, pindolol treatment resulted in a significantly higher rate of paresthesias and more intense nightmares and hallucinations than methylphenidate or placebo. In fact, because of these side effects, pindolol treatment was stopped after 32 patients had participated in the trial. Because of its side effect profile, use of pindolol for children with ADHD cannot be recommended.

TABLE 10 Pharmacokinetic Properties of Beta-Blockers (Adults)

Drug (brand name)	Selectivity	Lipophilicity	Peak effect (hr)	Plasma half-life (hr)	Elimination
Propranolol (Inderal)	None	High	1–1 ¹ / ₂	3–6	Hepatic
Atenolol (Tenormin)	β ₁	Low	2–4	6–9	Renal
Nadolol (Corgard)	None	Low	3–4	14–24	Renal
Metoprolol (Lopressor)	β ₁	High	1	3–4	Hepatic

Comparison of Propranolol with Other Beta-Blockers

See Table 10 for the pharmacokinetic properties of beta-blockers.

Chemical Properties

Propranolol (Fig. 2) and nadolol block both beta-1 and beta-2 receptors in the brain and peripherally. Atenolol and metoprolol selectively block beta-1 receptors and do not affect beta-2 receptors. Beta-1 receptors in the periphery are known to stimulate the heart chronotropically and ionotropically (Physicians' Desk Reference, 2001). Beta-2 receptors are found most commonly in brain glial cells and peripherally in the lungs and blood vessels, where they produce bronchodilation and vasodilation. At the present time the relative importance of the central versus peripheral effects of propranolol in the treatment of psychiatric disorders is not known. There is some evidence to suggest that the peripheral sympatholytic actions of propranolol may ameliorate anxiety and aggression more than its central activity (Coffey, 1990). Moreover, the beta-1 activity appears to be more involved in controlling anxiety and agitation than the beta-2 activity. Atenolol, a selective

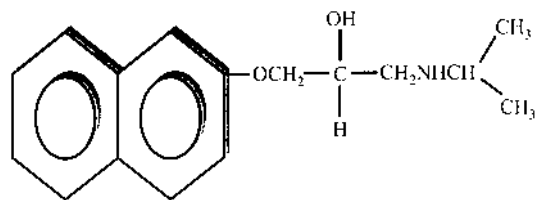


FIGURE 2 Molecular structure of propranolol.

beta-1 antagonist that penetrates the blood-brain barrier in only very small amounts, has been reported anecdotally to reduce agitation and anxiety in adults, while the selective beta-2 antagonists appear to have no obvious use in the treatment of behavior disorders.

Pharmacokinetic data in children and adolescents is lacking. Propranolol and metoprolol have prominent central and peripheral effects (Riddle et al., 1999). In contrast, atenolol and nadolol have prominent peripheral but not central effects. Propranolol and metoprolol are cleared by hepatic metabolism. In contrast, atenolol and nadolol undergo renal metabolism. Propranolol is very highly protein bound and undergoes a significant first-pass effect. In adults, propranolol exerts its peak effect 1–1½ hours after oral administration (Physicians' Desk Reference, 2001). Its serum half-life is 3–6 hours; therefore, it must be given more than once per day, unlike atenolol, which has a longer half-life and can often be given once per day (Coffey, 1990).

Indications

See Table 11 for indications for propranolol in children and adolescents.

Aggression in Brain-Damaged Children and Adolescents

In the early 1980s, several investigators reported on propranolol's effectiveness in the treatment of violent behavior in adult patients with organic brain disease

TABLE 11 Indications for Propranolol in Children and Adolescents

FDA-established indications:
None
Possible indications:
Aggressive patients with CNS damage
Lithium tremor
Akathisia
Performance anxiety (social anxiety disorder/social phobia)
Generalized anxiety disorder and panic disorder
Hyperventilation attacks
Alcohol withdrawal
PTSD
Seasonal affective disorder (winter depression)
Not indicated:
Schizophrenia
Tardive dyskinesia
Extrapyramidal side effects of neuroleptics (except akathisia)

(Yudofsky et al., 1981; Ratey et al., 1983; Greendyke et al., 1984). Williams and colleagues (1982) gave propranolol in an open-label fashion to 30 patients, 26 of whom were children and adolescents (age range 7–35 years). All subjects had exhibited uncontrolled rage and aggressive outbursts for at least 6 months and had failed to respond to other medications. Eighty percent of the children experienced moderate to marked improvement on a median dose of 160 mg of propranolol per day (range 50–1600 mg/day) (Williams et al., 1982). It should be noted that the highest daily dose of propranolol given was 1600 mg/day and that the patient tolerated this without hypotensive or other side effects. In fact, in the entire sample studied, side effects were minimal, with only one child becoming depressed. It is important to point out, however, that 22 of the patients were receiving additional psychotropic medications, such as antipsychotics, anticonvulsants, and stimulants, while receiving propranolol. Subsequent open-label studies have reported propranolol to be effective in treating refractory aggression, particularly in brain-damaged patients (Kuperman and Stewart, 1987; Grizenko and Vida, 1988). Lang and Remington (1994) reported the case of a 14-year-old with severe self-injurious behavior who was mentally retarded, blind, and deaf. They speculated that patients with mental retardation and associated motoric hyperarousal, self-injurious behaviors, and limited frustration tolerance might be especially responsive to propranolol. Nevertheless, with the lack of placebo-controlled study, no definitive conclusions can be declared at this time. Further study is necessary.

Posttraumatic Stress Disorder

Famularo and colleagues (1988) treated 11 hyperaroused, treatment-refractory PTSD children with propranolol in an open study. Propranolol was initiated at 0.8 mg/kg/day and increased gradually to a maximum of 2.5 mg/kg/day. The dosage was maintained at this level for 2 weeks and then gradually discontinued over the next 3 weeks. Side effects precluded raising the dose in only three children (Famularo et al., 1988). It is possible that lower doses of beta-blockers than those used in the treatment of anxiety disorders may be efficacious in the treatment of acute PTSD and that p.r.n. doses prior to stressful situations may be particularly effective. Studies in adults have not demonstrated superiority of propranolol over placebo in treating PTSD (Riddle et al., 1999). There are no controlled studies in children and adolescents.

Performance Anxiety (Social Anxiety Disorder/Social Phobia)

Propranolol has been reported to be effective in ameliorating performance anxiety in adult patients although no significant effects of beta-blockers over placebo have been observed in adults with social phobia (Liebowitz et al., 1992; Turner et al., 1994). Performance anxiety, known in lay terms as stage fright, is a relatively common social phobia. In addition to impaired performance, characteristic physical symptoms often arise, such as dry mouth, hoarseness, increased heart rate, and difficulty in breathing. Propranolol has minimal central side effects and may

improve performance (Arana and Hyman, 1991) in contrast to benzodiazepines, such as diazepam, which can cause sedation and so tend to worsen performance. In adults, a single dose of propranolol 10–40 mg 30–60 minutes before the anxiety-producing event has been reported to be effective. It is believed that many celebrities and performers take beta-blockers. It is wise to give a patient a test dose prior to a very important event to make sure that it helps and does not cause undue side effects in a particular patient. It should be underscored that controlled study has not found them to be superior to placebo in adults. There are also no placebo-controlled studies in children and adolescents.

Generalized Anxiety Disorder

When utilized in the treatment of adults with generalized anxiety disorders, propranolol has been found to be inferior to benzodiazepines and antidepressants (Kathol et al., 1980; Ratey et al., 1983; Arana and Hyman, 1991). Moreover, depressive disorders are common in such patients, and since one of propranolol's side effects is depression (see "Side Effects"), caution is advised when using this agent in this population of patients. Neppe (1989), however, reviewed 15 controlled studies of beta-blockers in the treatment of anxiety, 11 of which used propranolol, and determined that somatic anxiety (anxiety associated with cardiac and respiratory symptoms such as tachycardia and shortness of breath) responded well to these agents, while psychic anxiety (anxiety without somatic involvement) appears to be relatively unaffected by the beta-blockers. Gualtieri and colleagues (1983) point out that while beta-blockers are not the first-line treatment for anxiety disorders, they can provide a useful second-line or adjunct treatment in certain types of anxiety disorder. There are no data on children, but this may be an important area worthy of further investigation.

Panic Disorder

Propranolol and the beta-blockers have been found to be largely ineffective in the treatment of panic disorder (Neppe, 1989). In contrast to antidepressant drugs, which are effective in treating adult panic disorder, the beta-blockers do not reduce lactate-induced panic attacks (Gorman et al., 1983). In an open-label study, Joorabchi (1977) treated 14 adolescents with hyperventilation syndrome with propranolol 10–30 mg/day and noted that 13 of the 14 patients appeared to benefit from this treatment. He suggested that propranolol might, therefore, be effective in treating panic disorder. There are no controlled studies in children and adolescents, and because of their lack of efficacy in adults with panic disorder, their use in this population is not recommended.

Akathisia

Many clinicians believe that beta-blockers such as propranolol are the drugs of choice for neuroleptic-induced akathisia in adults (Lipinski et al., 1984; Ratey et al., 1985; Adler et al., 1986). When akathisia is particularly refractory, or when

extrapyramidal side effects coexist with the akathisia, propranolol can be given together with benzodiazepines or anticholinergic agents (Arana and Hyman, 1991) (see Chapter 12). Propranolol is given at doses of 30–80 mg/day to treat akathisia and seems to work quickly once an effective dose is reached. It appears to have no effect on other parkinsonian symptoms. Alpert and colleagues (1990) observed a significant improvement in both akathisia and aggression when nadolol was added to the treatment regimen of patients receiving antipsychotics, lending further support to the contention that a peripheral mechanism is responsible for the improvement in aggression and akathisia, that is, the decrease in hyperarousal. There are currently no data in children and adolescents. In children, where it is often difficult to differentiate akathisia from hyperactivity, beta-blockers are generally not recommended. Conservative measures, such as adjusting the antipsychotic medication, are preferred.

Lithium Tremor

Tremor is frequently seen in patients treated with lithium (see Chapter 13). The coarse tremor associated with lithium toxicity is particularly bothersome and easy to notice. Often, however, the fine tremor associated with therapeutic blood levels can be annoying and troublesome to patients. Before propranolol is initiated, it is important to make sure that the patient is on the lowest possible effective dose of lithium. Decreasing the dose may ameliorate the tremor to a sufficient degree so that it is no longer a problem, while still treating the psychiatric symptoms. In adults, tremor can be reduced by decreasing or eliminating caffeine consumption. Campbell and associates (1984), however, observed that although tremor was an untoward effect associated with lithium administration in children, it did not appear to be clinically significant and did not interfere with functioning. We do not recommend propranolol for the treatment of lithium-induced tremor in children and adolescents.

Seasonal Affective Disorder (Winter Depression)

Since beta-blockers suppress melatonin, propranolol and atenolol have been used to treat winter depression (Schlager, 1994; Riddle et al., 1999). There are no data in children and adolescents and the impact of neuroendocrine manipulation on childhood development is not known. Further study is clearly warranted.

Alcohol Withdrawal

See Chapter 19 for a discussion of the treatment of substance abuse disorders.

Schizophrenia

High doses of propranolol of up to 4000 mg/day have been used to treat patients with schizophrenia without demonstrable benefit (Arana and Hyman, 1991).

There are no data on children and adolescents. Because of its lack of efficacy in adults, its use in children and adolescents is not recommended.

Tardive Dyskinesia

Beta-blockers have been tried in the treatment of tardive dyskinesia in adults, but have not been found to be effective (Arana and Hyman, 1991). There are no data on children and adolescents, but because of their lack of efficacy in adults, their use in children and adolescents is not recommended.

Contraindications

See Table 12 for contraindications to propranolol use.

Diabetes and Hypoglycemia

Propranolol is contraindicated for patients with diabetes. Particular caution is necessary in diabetics prone to hypoglycemia since beta-blockers may interfere with normal response to hypoglycemia (Gualtieri et al., 1983).

Bronchospastic Disease

Propranolol is contraindicated for children and adolescents with bronchospastic diseases such as asthma (Gualtieri et al., 1983). Some clinicians believe that for patients with bronchospastic disease, selective beta-1 antagonists such as atenolol are preferable. It is important to remember, however, that even beta-1 selective agents have some risk of exacerbating the respiratory condition. Since there are few controlled studies assessing the efficacy of the beta-blockers, including the selective beta-1 agents, in psychiatric disorders, the risks of using any of these agents outweigh their potential benefits. Therefore, we strongly recommend avoiding the use of beta-blockers for children and adolescents with bronchospastic disease.

TABLE 12 Contraindications to Propranolol Use

Bronchospastic disease (asthma)
Diabetes/hypoglycemia
Allergic reaction
Medicated with MAOI
Hyperthyroidism
Depression
Pregnancy

Cardiovascular Conditions

Propranolol is contraindicated for children and adolescents with heart disease (Coffey, 1990). It is, therefore, important to screen all patients for cardiovascular pathology by checking vital signs, giving them a physical examination, and taking a cardiogram before initiating treatment with propranolol.

Hyperthyroidism

Propranolol should generally be avoided in children and adolescents with hyperthyroidism (Gualtieri et al., 1983; Coffey, 1990).

Depression

In general, propranolol should be avoided for children and adolescents with a depressive disorder, a history of depression, and/or a strong family history of affective disorders. A selective beta-1 antagonist such as atenolol may be indicated for these patients (Coffey, 1990). Atenolol may pose less of a risk for the development of depression than propranolol, possibly because of its poor penetration of the blood-brain barrier (Coffey, 1990), although its use can be associated with depression.

Children and adolescents with anxiety disorders pose a dilemma. Patients with such disorders have a higher occurrence of comorbid depressive disorders than the general population. It may behoove the clinician in this instance to recommend the use of atenolol instead of propranolol.

Pregnancy

There is virtually no psychiatric indication for propranolol or any beta-blocker's use during pregnancy.

Patients on MAOIs

Propranolol and the other beta-blockers are absolutely contraindicated for children and adolescents receiving MAOIs (Gualtieri et al., 1983).

History of Allergic Reaction

As with any medication, a history of allergic reaction to the beta-blockers precludes their use.

Side Effects

See Table 13 for side effects of propranolol.

Decreased Heart Rate

Propranolol can decrease the pulse to less than 50 beats per minute (Gualtieri et al., 1983; Neppe, 1989; Coffey, 1990). It is, therefore, essential to get baseline vital signs and monitor cardiovascular function while the patient is on propranolol.

TABLE 13 Side Effects of Propranolol

Common:
Decreased heart rate
Raynaud's phenomenon
Lethargy
Impotence
Uncommon:
Bronchoconstriction
Congestive heart failure
Depression
Hallucinations
Rare:
Hypoglycemia
Hypotension/dizziness
Nausea/diarrhea
Vivid dreams and nightmares
Affect growth hormone regulation
Suppression of melatonin

olol. It is best to increase the dose gradually in children and adolescents. This medication should never be stopped abruptly, and gradual tapering is indicated to avoid problematic rebound hypertension (Riddle et al., 1999). Bradycardia is much less likely to occur when atenolol is used instead of propranolol (Coffey, 1990).

Raynaud's Phenomenon

Propranolol administration, by decreasing peripheral circulation, can lead to the development of Raynaud's phenomenon, which is characterized by tingling, numbness, and pain in the fingers (Coffey, 1990).

Tiredness and Weakness

Patients treated with propranolol rather commonly experience the side effects of tiredness and weakness (Coffey, 1990).

Sexual Impotence

Impotence is considered a common side effect of propranolol (Coffey, 1990).

Congestive Heart Failure

This is a relatively uncommon side effect of propranolol, and the risk is extremely low for those without preexisting cardiovascular disease (Coffey, 1990).

Bronchoconstriction

Bronchoconstriction is a relatively uncommon but very serious and potentially life-threatening side effect of propranolol. It is believed to be less common with atenolol (Coffey, 1990), but as we have pointed out, we recommend immediate discontinuation of all beta-blockers when this side effect is encountered since the risks outweigh the potential benefits. Bronchoconstriction is an important concern in asthmatic children so that propranolol should not be prescribed to children with asthma.

Depression

Depression is a potentially serious side effect of propranolol treatment and appears to be less of a problem when atenolol is used instead of propranolol (Coffey, 1990). We recommend discontinuing propranolol in depressed patients and switching to atenolol.

We do not subscribe to the view held by some clinicians that depression induced by propranolol can be treated with an antidepressant, thus obviating the need for discontinuing propranolol. Since beta-blockers have not been proved to be effective for any child or adolescent neuropsychiatric condition, we believe that their use in a depressed child is not warranted and exposes the patient to the risk of polypharmacological side effects. Depression as a result of beta-blocker administration requires discontinuation of the beta-blocker and not treatment with an antidepressant. Should the depression persist after the beta-blocker is withdrawn, antidepressant administration may be warranted.

Hallucinations

Hallucinations are an uncommon side effect of propranolol that has rarely been reported (Coffey, 1990). It is believed to be practically nonexistent in patients treated with atenolol. They may be especially problematic in children treated with pindolol (Buitelaar et al., 1996).

Hypoglycemia

Hypoglycemia is a rare side effect and, as mentioned, is mainly of concern in diabetic patients (Coffey, 1990).

Growth Hormone Regulation

Beta-blocker administration may impact on growth hormone (GH) regulation (Riddle et al., 1999). While when administered alone, beta-blockers do not stimulate GH secretion (Riddle et al., 1999), chronic administration of atenolol has been shown to potentiate growth-promoting effects of GH-releasing hormone treatment in children with growth deficiencies (Cassorla et al., 1995).

Hypotension/Dizziness/Nausea/Diarrhea

These problems are occasional side effects of propranolol (Coffey, 1990).

Vivid Dreams and Nightmares

Sleep disruption is an occasional adverse side effect of propranolol (Coffey, 1990). When insomnia and nightmares appear, propranolol is most frequently the beta-blocker being administered, since these problems appear to be almost nonexistent with the other beta-blockers (Coffey, 1990).

Overdose and Toxicity

Beta-adrenergic blockade can be a medical emergency, resulting in bradycardia, hypotension, cardiac arrest, and respiratory distress (Coffey, 1990). Gastrointestinal symptoms such as nausea and diarrhea may also be experienced. Peripheral cyanosis, psychosis, and seizures may occur after overdose.

Propranolol is not dialyzable, and when a patient overdoses, immediate evacuation of gastric contents is necessary. When bradycardia occurs, atropine 0.25–1.0 mg should be administered. If there is no response to vagal blockade, cautious administration of isoproterenol is recommended (Arana and Hyman, 1991; Physicians' Desk Reference, 2001). In the event of cardiac failure, digitalization and diuretics are necessary. In the event of hypotension, vasopressors such as epinephrine are indicated. When bronchospasm is encountered, the administration of isoproterenol and aminophylline is necessary (Arana and Hyman, 1991; Physicians' Desk Reference, 2001).

Abuse

There appears to be relatively no risk for the recreational abuse of propranolol.

Drug Interactions

Because propranolol is highly protein bound, drug interactions (Table 14) may be problematic. Beta-blockers can increase or decrease the effects and levels of certain drugs through competitive inhibition (Riddle et al., 1999). Propranolol has been shown to inhibit tricyclic antidepressant metabolism, and this combination has resulted in nearly toxic imipramine levels in two children (Gillette and Tannery, 1994).

Available Preparations and Cost

See Table 15 for preparations and cost of propranolol and atenolol.

Initiating and Maintaining Treatment

The practicing clinician who decides to start propranolol must ensure that the child or adolescent has a comprehensive baseline history and a physical exam-

TABLE 14 Drug Interactions

Propranolol may increase effects of:

- Anesthetics
- Antipsychotics
- Calcium blockers
- Clonidine
- Epinephrine
- Lidocaine
- MAOIs
- Phenytoin
- Thyroxine
- Tricyclic antidepressants

Propranolol may decrease effects of:

- Insulin
- Oral hypoglycemia

Drugs that increase effect of propranolol:

- Cimetidine
- Molindone

Drugs that decrease the effect of propranolol:

- Carbamazepine
- Estrogens (birth control pills)
- Nicotine
- Nonsteroidal anti-inflammatory analgesics

When used together, shared inhibition of propranolol and:

- Aminophylline
- Narcotic analgesics
- Sympathomimetics
- Theophylline

TABLE 15 Available Preparations and Cost

Drug	Preparations	Average cost/day
Propranolol	Generic (scored tablets): 10, 20, 40, 60, 80, 90 mg Inderal: 1 mg/mL injectable	\$0.11
Atenolol	Tenormin (scored tablets): 50, 100 mg	\$0.74

Source: *Red Book Annual Pharmacist Reference, 1989–1990*. Oradell, NJ: Medical Economics.

ination. Documentation of normal cardiovascular function must be obtained. Baseline vital signs must also be obtained, and careful monitoring of cardiovascular functioning must be implemented while the child or adolescent is receiving propranolol. Starting with low-dose propranolol and increasing the dose gradually to ensure that blood pressure and pulse drop as little as possible is advisable. If the blood pressure decreases to below 90/60 mmHg and/or if the pulse falls to less than 60, the next dose of propranolol should not be given (Coffey, 1990). Consideration of decreasing subsequent dosages of propranolol is indicated. An ECG should be performed. If there is any abnormality or if the vital signs do not return to normal, consultation with a cardiologist is advisable.

As was mentioned earlier, if the child or adolescent with a psychiatric disorder has asthma or a potential for asthma, propranolol is contraindicated since its safety has not been established in this population. If the child develops an asthmatic condition while on propranolol, the medication must be discontinued immediately and the asthma treated appropriately. The propranolol should not be reinstated once the asthma attack subsides. We also believe that all beta-blockers, regardless of selectivity, should be avoided in such patients.

The hypoglycemic side effects of propranolol usually do not require any intervention in patients who are not diabetic (Coffey, 1990). Propranolol should be avoided, however, if the patient has a history of diabetes. When there is a family history of diabetes, propranolol is not absolutely contraindicated, but fasting blood sugars and a glucose tolerance test are recommended to evaluate fully how much risk is involved (Coffey, 1990). When there is doubt or concern, we recommend avoiding propranolol. It would be our recommendation, for example, that a child with a significant family history of diabetes and normal fasting blood sugars and glucose tolerance tests be started on atenolol rather than propranolol. In the event of any abnormality of the fasting blood sugar and/or glucose tolerance test, we advise using another medication and avoiding beta-blocking agents. If the clinician feels that a beta-blocker is essential to treatment, consultation with the child or adolescent's medical doctor is strongly recommended.

It is also important to inform both male and female adolescents about the risk for sexual dysfunction with propranolol, since this is a relatively common side effect. It is important to talk with the adolescent prior to starting the medication and to monitor this during treatment. Moreover, the female adolescent should be asked about sexual activity and her chances of becoming or plans to become pregnant.

It is important to monitor closely for propranolol-induced depressive side effects. It is particularly important to determine whether there is a personal or family history of depression. It is best to avoid using propranolol for these children and adolescents. Atenolol may be a better choice in such patients. When

depressive side effects are encountered during propranolol therapy, switching to atenolol may be warranted since this agent is less commonly associated with depression, probably because of its poor penetration of the blood-brain barrier. We do not recommend the initiation of antidepressant therapy in combination with propranolol for these children and adolescents. Instead, we recommend tapering and discontinuing the propranolol and starting an antidepressant only if the depression is sufficiently severe that treatment cannot be delayed or if the depression persists after propranolol discontinuation.

The sleep disturbances that are occasionally seen with propranolol use can often be easily ameliorated by changing the time of the last daily dose of the medication to earlier in the day (Coffey, 1990).

Clinical Practice: Dosage and Administration

No firm guidelines have been established for the dosing and administration of propranolol and the other beta-blockers in child and adolescent psychiatry, nor has any age limit been specified for their use. But since these agents have been utilized in the treatment of many medical disorders, there are some guidelines that may be appropriate for psychiatric patients as well (Forsythe et al., 1984). The normal dose range for adolescents treated with propranolol is 20–300 mg/day (Coffey, 1990). The dose is generally started at 10 mg two times per day and increased by 10–20 mg every 3–4 days. Prepubertal children are usually started on a dose of propranolol of 10 mg/day, with the dose being increased by 10 mg increments every 3–4 days (Coffey, 1990). The normal dose range for these children is 10–120 mg/day. No one has determined the maximal dose for children and adolescents. The FDA guidelines for the dose limit for propranolol in the treatment of medical conditions affecting adults and children is 16 mg/kg/day for children and 640 mg four times per day for adults (Forsythe et al., 1984). Even less information exists on the use of atenolol. Here, the FDA guidelines for the treatment of medical disorders have set a dose limit of 200 mg four times per day in adults. There is no specification for children.

Withdrawal of propranolol in children and adolescents should be done gradually, especially if the patient has been receiving the medication chronically. Rebound sympathomimetic side effects such as hypertension, tachycardia, and arrhythmias have been reported in adult patients with cardiac disorders when propranolol is abruptly discontinued after chronic use (Coffey, 1990). Although these risks appear to be less in healthy children and adolescents as compared with adult cardiac patients, caution is recommended, particularly if the child or adolescent is being treated as an outpatient and where close monitoring is more difficult. Generally, the patient should be withdrawn by 10–20 mg decrements every 3–4 days, making sure that vital signs remain stable.

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17

Atypical and Adjunctive Agents

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Nonstandard psychoactive drugs, such as vitamins, opiate antagonists, exogenous hormones, and herbal medications, are gaining increasing attention in adult and childhood psychiatric disorders. Both patients and practitioners have become more familiar with data supporting or refuting the use of these agents in children. It is beyond the scope of this chapter to cover the entire range of atypical psychopharmacological agents in any great detail, as nontraditional medications constitute today a unique and complex segment of clinical pharmacology. Only treatments that have received some degree of experimental scrutiny will be covered in this chapter, including opiate antagonists, nutritional therapy, high-dose vitamin therapy, and thyroid hormone analogs. Given the great increase in the use of herbal medications and dietary supplements over the past decade, these products will be covered in a separate section in the second half of this chapter.

OPIATE ANTAGONISTS

Opium, the oldest psychotropic medication, was considered indispensable by Greek physicians. Its earliest recorded use dates back to Mesopotamia around 5000 B.C. (Alexander and Selesnick 1966; Thompson and Schuster 1968). The modern use of opium derivatives is limited to analgesic agents (morphine, meper-

idine, codeine) and drugs of abuse (heroin). The study of opiate antagonists began with the use of nalorphine as an antidote to intoxication with opium derivatives (Thompson and Schuster 1968). Naloxone (Narcan™) and other parenteral opiate antagonists were later used as tools to study the role of endogenous and exogenous opiates and hormonal and endocrine functions (Vargas et al. 2000) in animals. Naloxone was marketed for human use to treat iatrogenic and recreational opiate toxicity (see Chapter 19). However, several behavioral effects suggested other uses for the drug. Animal studies showed that opiate antagonists reverse the hyperphagia and obesity associated with elevations in endogenous opiate levels (O'Brien et al. 1982), decrease social aggression (Lynch et al. 1983), and attenuate drug- or stress-induced stereotypy (Cronin et al. 1985; Skorupska et al. 1989). These observations, along with the availability of an oral opiate antagonist (naltrexone), led to studies for the treatment of obesity, eating disorders, autistic disorder, and self-injurious behavior.

Chemical Properties

Absorption and Metabolism

Two forms of opiate antagonist are used in psychiatry: parenteral naloxone (Narcan™) and oral naltrexone (Trexan™). Naloxone may be administered intravenously or intramuscularly, and the onset of action from either route occurs within minutes. Oral naltrexone is variably absorbed and reaches peak concentrations in one hour, with >90% of the drug being converted to active (6-beta-naltrexol) and inactive metabolites. The approximate mean elimination half-lives for naloxone and naltrexone in adults are 1 and 4 hours, respectively. 6-Beta-naltrexol has a half-life of 12.9 hours. The half-life of naloxone in children is not well studied (PDR 1993).

Mechanism of Action

Opiate antagonists block the effects of exogenous opiate derivatives (Chabane et al. 2000). Morphine-like substances (endorphins and enkephalins) are present naturally in the brain and are released during times of physical pain or stress, accounting for the phenomena of posttraumatic analgesia and euphoria following intense exercise. Models of dysregulation of endogenous opioids and suprathreshold for pain (Sandman 1988) have been postulated in the pathogenesis of self-injurious behavior (SIB). The theoretical basis for the explained mechanism of action of opiate antagonists essentially posits that children with autistic disorder would have a higher threshold to pain and intrinsic opioid "substimulation," driving their SIB as an indirect mechanism for release of endogenous opioids. Opioid antagonists therefore would interrupt this loop, exerting a therapeutic effect (Sandman 1988). However, their precise mechanism of action in the treatment of SIB in autistic disorder remains unknown (Schroeder et al. 2001).

Indications

Opiate antagonists have FDA approval for psychiatric disorders involving intoxication with opiate drugs. Empirically they have been used for the treatment of hyperactivity and SIB in children with pervasive developmental disorders (PDD) and mental retardation (MR) (Aman et al. 2000).

Self-Injurious Behavior

Self-injurious behavior is a symptom that cuts across several psychiatric disorders, especially developmental disabilities, mental retardation, and autistic disorder (Schroeder et al. 2001). The underlying biological mechanism of SIB has been indirectly related to dopaminergic pathways, as shown in behavioral phenotypic conditions such as Lesch-Nyhan syndrome (Wong et al. 1996), and to opioid receptor systems in autism (Leboyer et al. 1993). Several placebo-controlled studies have reported reduction of SIB with naloxone or naltrexone treatment, but these have been conducted on very small samples and have been of short duration (Taylor and Kobak 2000). Sandman and colleagues were among the first to report open (Sandman et al. 1990) and controlled (Sandman et al. 1983) observations of dose-dependent reduction of SIB in adults with mental retardation. In all subjects stereotypy was slightly increased and hyperactivity measures were unaffected (Sandman et al. 1987). Subsequently, controlled (Barrett et al. 1989; Kars et al. 1990) and uncontrolled (Herman et al. 1987) reports of samples ranging from one (Walters et al. 1990a) to six (Kars et al. 1990) subjects showed equivocal results. The majority of these studies (Herman et al. 1987) reported a therapeutic effect for the treatment of SIB with opiate antagonist, but methodological differences and deficiencies prevail. Among the negative reports (Davidson et al. 1983; Beckwith et al. 1986), Szymanski and colleagues (1987) found that 50 or 100 mg of naltrexone under double-blind conditions had no effect on the SIB, self-stimulatory, or agitated behavior in two young adults with mental retardation. In summary, there is equivocal evidence in support of the treatment of SIB in youngsters with opiate antagonists. Although 15 subjects improved significantly in a controlled cumulative sample of 24 subjects, only one controlled case has reported successful treatment of SIB for 6 months (Walter and Rey 1999). Demonstration of long-term clinical benefit is essential, since SIB typically persists for years and the possibility of tolerance to opiate antagonism is uncertain. Opiate antagonists may be effective in a subset of patients with SIB (Szymanski et al. 1987). This subgroup could be differentiated with larger studies using variable, weight-adjusted doses of naltrexone.

Hyperactivity in Youngsters with PDD

The effect of naltrexone for the treatment of hyperactivity in youngsters with PDD is overall more promising than the treatment of SIB. Five controlled studies

(Campbell et al. 1993; Kolmen et al. 1995; Willemsen-Swinkels et al. 1995a; Kolmen et al. 1997; Willemsen et al. 1999) have shown evidence of improvement as measured by standard scales such as the Conners Parent and Teacher Rating Scales, and the Aberrant Behavior Checklist (Aman et al. 2000). For an excellent review of the subject, the reader is referred to Aman and colleagues (2000).

Autistic Disorder

Autistic children have characteristics that have been loosely compared to opiate intoxication (Kalat 1978). Social withdrawal, stereotypies, and sensory hyper- or hyposensitivity lead to the hypothesis that endogenous opioids could play an etiological role in autism (Deutsch et al. 1977; Kalat 1978). More compelling are the effects of opiate drugs on the early social development of animals. Morphine reduces maternal/offspring separation distress and attachment in young mammals and chicks (Herman and Panksepp 1978; Panksepp and Lensing 1991) and decreases social exploratory behavior without affecting nonsocial exploratory behavior in young rodents (Landaver and Balster 1982). These observations supported a rationale for conducting studies in children with autistic disorder (Sahley and Panksepp 1987).

The first systematic study of naltrexone in autistic children was conducted by Campbell and associates (Campbell et al. 1988a). Ten children aged 3–7 years were treated with 0.5, 1.0, or 2.0 mg/kg/day in open trial with structured outcome measures. The results indicated improvements in some autistic (withdrawal, unproductive speech, and stereotypy) and nonautistic symptoms (restlessness and tantrums). The only adverse effect was mild sedation (Campbell et al. 1978, 1990). This group repeated this study in 18 autistic children (aged 3–8 years) under double-blind conditions. The treatment group improved significantly on a global assessment scale, but not on the specific symptom scales employed in the earlier studies. Social withdrawal and communicative speech were the areas that showed the most consistent improvements (Campbell et al. 1988b). One subsequent open trial replicated similar effects in four children with autistic disorder which persisted up to one year (Panksepp et al. 1980). One randomized, double-blind, placebo-controlled crossover of 13 children with autistic disorder (mean age 5.4 years) treated with naltrexone, 1.0 mg/kg daily, only modestly replicated previously reported improvement of behavior and social communication in young children with autism (Kolman et al. 1995). Furthermore, in a double-blind, placebo-controlled crossover trial, Willemsen-Swinkels and colleagues treated 23 autistic children with a single 40 mg dose of naltrexone, failing to produce significant changes in social behavior, but reducing irritability and indices of activity and attention on behavior checklists (Willemsen-Swinkels et al. 1995a). Similarly, the effect of naltrexone on communication skills of young children with autism was recently evaluated in 24 children with autism (mean age 5.1 years) by Feldman and colleagues (Feldman et al. 1999). Subjects participated in a ran-

domized, double-blind, placebo-controlled, crossover trial of naltrexone, 1.0 mg/kg, or placebo for 2 weeks. Communication was evaluated from videotaped samples of parent-child interaction. No differences were found between the naltrexone and placebo conditions in any of the measures of children or parent communication, suggesting that naltrexone does not lead to acute improvement in communication, a core deficit of autism.

In summary, although Campbell et al. (1988a, b, 1990) had previously suggested that naltrexone may improve “core” autistic symptoms such as social withdrawal and communicative speech, these findings were not replicated (Willemssen-Swinkels et al. 1995a; Feldman et al. 1999). A more reliable therapeutic effect may be evident in the treatment of hyperactivity and perhaps SIB (Barrett et al. 1989; Walters et al. 1990a) in these youngsters (Chavane et al. 2000). Naltrexone appears to be safe in doses of 0.5–1.0 mg/kg/day. Interestingly, the opioid “addiction” hypothesis would predict that treatment would have the greatest effect on social development when started at a young age. This was not observed by Campbell and colleagues (1988b), who noted the greatest symptomatic improvement in older autistic children. Further controlled comparison of the effects of naltrexone across age groups is desirable.

Obesity and Eating Disorders

Opiate antagonists inhibit hyperphagia in some strains of genetically obese rodents and rodents with high endogenous opioid levels (Kyriakides et al. 1980). This effect was initially noted in patients with Prader-Willi syndrome (Kyriakides et al. 1980) and patients with obesity (Atkinson et al. 1985) and bulimia (Sternbach et al. 1982), but later studies did not support these findings (Zipf and Berntson 1987; Mitchell 1993; Mitchell et al. 1989). Although several authors have suggested that a subset of bulimics with abnormal endorphin levels may respond to opiate antagonists (Jonas and Gold 1986–1987, 1987; Alger et al. 1991; Jonas 1998), current data do not support the clinical use of naltrexone to treat these disorders in humans (de Zwaan and Mitchell 1992). Conversely, recent animal studies involving melanocortin peptide analogs suggest that these peptides may have anorectic effect (Vergoni and Bertolini 2000), justifying further studies to clarify the links between the endogenous opioid system and feeding behavior (Johnson 1995).

Side Effects

In the studies cited above, mild sedation was the only reported adverse effect in children. The manufacturer of naltrexone and naloxone (DuPont) also reports mild hepatic toxicity at high doses, but not at doses that effectively block opioid receptors. Insomnia, anxiety, and gastrointestinal upset are listed as infrequent side effects but have not been reported in clinical studies. Abuse and dependence

to these agents are not described. There are no reported cases of overdose (PDR 2001).

Available Preparations and Cost

Naloxone is available only as an injection; therefore, its outpatient use is potentially very limited. Naltrexone (Trexan™) is available only as 50 mg tablets with an average wholesale price of \$209.40 per 50 tablets. Since the most effective dose for both SIB and autistic disorder appears to be 1.5 mg/kg/day, a 50 kg child would require approximately 75 mg/day at a (wholesale) cost of \$6.29. An 80 kg adult would require approximately 125 mg at a cost of \$10.48 per day (PRG 1992).

Initiating and Maintaining Treatment

Clinical use of naltrexone for SIB and autistic disorder is not FDA approved but may be acceptable in treatment-resistant cases based on the results of preliminary trials and the apparent safety of this agent in children (Herman et al. 1989). The use of opiate antagonists in substance abuse disorders is discussed elsewhere (Chapter 19). If prescribed, a small test dose of naltrexone should be administered before treatment, followed by close observation for signs of opiate withdrawal. Baseline and periodic liver function studies are recommended. The drug should be discontinued in the unlikely event of hepatic toxicity.

The manufacturer does not provide dosing guidelines for children, since naltrexone is not approved for use in patients under 18 years of age. Available studies suggest that some autistic children and children with SIB would respond to doses of 0.5–1.0 mg/kg/day (Kolmen et al. 1997). Since lower doses have not been tested, a starting dose of 0.25 mg/kg/day, with gradual increases every 1–2 weeks, could be prudent. The 50 mg scored tablet may be quartered or crushed to allow for fine increments. The largest study of naltrexone in autism thus far (Campbell et al. 1993) used 1.0 mg/kg/day administered in a single morning dose over a period of 3 weeks (and was associated with a significant reduction in hyperactivity). Therefore, this should be considered the maximum dose until further studies are available.

Nutritional Therapy

The motivation for developing nonpharmaceutical treatments for child and adolescent emotional illness is high. Such therapies are attractive because they do not carry the social stigma that accompanies the use of mood-altering drugs in children. Nutritional therapy in particular is advocated as a more natural alternative to medication and has seen a plethora of uncontrolled and controlled studies emerge in the past few years.

Attention-Deficit Hyperactivity Disorder

Feingold (1973, 1975) and others (Mattes 1983; Rowe 1988) hypothesized that hyperactivity could result from allergic reactions to food additives and natural salicylates, nevertheless, a naturalistic study failed to detect a difference in the diets of hyperactive and nonhyperactive children (Kaplan et al. 1989). Moreover, Connors reviewed the uncontrolled positive studies and the negative controlled ones and concluded that, at best, food factors were involved in only a few cases (Cronin et al. 1985). Although this group reported that each class of dependent measures was found to be sensitive to nutritional manipulations, under double-blind conditions both sucrose and fructose produced a significant increase in motor activity and inappropriate behavior compared to an aspartame placebo (Connors and Blouvin 1982–1983). Similarly, a beneficial effect of eliminating reactive foods and artificial colors in children with ADHD was reported in 16 atopic children with attention-deficit hyperactivity disorder (ADHD) (Boris and Mandel 1994). Despite these two positive studies, dietary interventions in children with ADHD have not been proved to be efficacious on any definitive controlled study (Wolraich 1998), making their potential therapeutic effect a source of ongoing debate among the general public (Barbaresi and Olsen 1998).

High-Dose Vitamin Therapy

Although deficiencies of pyroxidine (vitamin B₆) (a cofactor in amino acid metabolism) and niacin (vitamin B₃) (a nicotinamide adenine dinucleotide coenzyme) may produce neuropsychiatric symptoms, including nerve degeneration, seizures, delirium, psychosis, and dementia (Menolascino et al. 1988), studies on nutritional status in childhood psychiatric disorders have not found correlations to vitamin deficiencies (Siva Sankar 1979).

Vitamins given at pharmacological doses (“megavitamin” or “orthomolecular” therapy) are a strategy that received a great deal of attention in the early 1970s. Linus Pauling was a visible proponent for the use of high-dose vitamin C in viral infection and psychiatric disorders (Pauling et al. 1974; Pauling 1979). His influence may have been important in the exploration of vitamin therapy treatments in ADHD, schizophrenia, and autism. Despite an expanding body of literature on the subjects of nutrition and brain function, the uncontrolled data are embedded in nonclinical journal or letters to the editor (Greenblatt 1999) awaiting further scientific evidence regarding their effectiveness in child psychiatric disorders.

Attention-Deficit Hyperactivity Disorder

High doses of vitamin A and others have been proposed for treatment of ADHD. Few controlled studies are available that both standardize pretreatment diagnosis and use objective outcome measures. However, two well-designed and controlled

trials with a cumulative sample of 72 hyperactive children showed no improvement based on objective outcome measures (Arnold et al. 1978; Haslam et al. 1984). On the contrary, there was a statistically significant 25% *increase* of disruptive classroom behavior in children treated with a combination of vitamin B₆, vitamin C, niacin, and calcium pantothenate (Haslam et al. 1984). Severe toxicity of vitamin A has been reported in children treated for ADHD (Shaywitz et al. 1977). In their review of 53 trials of megavitamin therapy, Kleijnen and Knipschild concluded that there was no evidence for a therapeutic effect of vitamin B₆ in ADHD, certainly not sufficient to warrant the risk of toxicity (Kleijnen and Knipschild 1991).

An additional study involved 11 hyperactive boys treated for 2 weeks with D-phenylalanine (20 mg/kg/day) and for 2 weeks with placebo in a double-blind crossover study. Tests included parent and teacher behavior ratings, cognitive measures, and blood and urine measures of norepinephrine, amino acids, and trace amines. No significant improvement or deterioration in behavior and no side effects were noted, and only serum phenylalanine was increased by the active treatment phase. This provides reassurance about the toxicity of aspartame, a food additive that contains phenylalanine, but argues against precursor loading treatment of hyperactivity (Zametkin et al. 1987).

Schizophrenia

A theoretical vitamin regimen was proposed for the treatment of schizophrenia in one of the first applications of orthopsychiatric methods (Pauling et al. 1974; Ban et al. 1977). The use of high-dose niacin and vitamin B₆ was vigorously tested between 1955 (Okawa et al. 1998) and 1977 (Deutsch 1986), and case reports of vitamins B₆ and B₁₂ in both adult and child schizophrenics have appeared (Denson 1976; Brooks et al. 1983). In their broad review of all controlled trials, Kleijnen and Knipschild (1991) found no evidence for the efficacy of vitamin therapy in schizophrenia. No study since 1970 has shown a significantly positive result, and no study with follow-up longer than 3 months has ever shown a significant positive result (Kleijnen and Knipschild 1991). There is stronger support for including folate at physiological doses when red cell folate is demonstrated to be low or marginal (Godfrey et al. 1990). However, this must be considered an appropriate correction of vitamin deficiency, rather than a specific treatment.

Fragile X Syndrome

Unlike the other megavitamin therapies, there is some heuristic support for treatment of fragile X syndrome with folic acid. The fragile X defect is revealed *in vitro* in chromosomes cultured in a folate-free medium, and the percentage of cultured cells expressing the fragile X site may be reduced by folate enrichment

(Gillberg et al. 1986). Sporadic reports of improved mentation or behavior in vivo were followed by a number of controlled studies that showed no significant group effect (Brown et al. 1986; Gillberg et al. 1986; Hagerman et al. 1986; Madison et al. 1986). When Fisch and colleagues (1988) used non-fragile X control subjects, there was no difference in behavior on folic acid (Fisch et al. 1988). The positive results may, therefore, be attributed to nonblind, noncontrolled study designs.

Autism

Rimland and associates (1978) conducted the first controlled study of vitamin B₆ in autism after successful case reports appeared. They reported statistically significant improvement in behavioral measures of 15 children on 3 g/day of pyridoxine. This study has been criticized on the grounds that few of the children studied met research criteria for autism, the sample was preselected for sensitivity to vitamins (Moss and Boverman 1978), behavior ratings were not entirely reliable, and concomitant medications not specified (Pfeiffer et al. 1995). One other controlled trial of vitamin B₆ in children with autism replicated significant improvement in behavior (Martineau et al. 1985). Nevertheless, a review article by Pfeiffer et al. (1995) presented a critical analysis of 12 published studies of vitamin B₆ and magnesium in the treatment of autism. Although the majority of studies report a favorable response to vitamin treatment, the authors concluded that the interpretation of these positive findings needed to be tempered because of methodological shortcomings in many of the studies. Despite employing double-blind procedures in 50% of the studies, a number of studies employed imprecise outcome measures, measured dosages in different units (mg/day or mg/kg/day) across studies, reported changes in urinary output of homovanillic acid (HVA) following B₆-Mg administration, a measure that may reflect changes in diet or renal excretion rather than changes in central nervous system (CNS) dopamine function, and did not adjust for regression effects in measuring improvement (Pfeiffer et al. 1995).

Recently, a 15-year follow-up of a boy with pyridoxine (vitamin B₆)-dependent seizures and autism was reported (Burd et al. 2000), noticing that pyridoxine dependency is a rare autosomal-recessive disorder that can present with a severe seizure disorder of neonatal onset and autism. Fewer than 100 cases have been reported, and most of these patients require lifelong treatment with pyridoxine (Burd et al. 2000).

Mental Retardation

Reports of increased IQ scores after vitamin supplementation generated an enthusiastic response from the media 10–15 years ago. One double-blind trial in a group of 16 mentally retarded children (IQ range 17–70) treated with 4 months

of broad vitamin supplementation reported a mean IQ gain of 10 points (Harrell et al. 1981). They also noted improved visual acuity and increased growth rates in two children. However, several methodological problems of this study cannot be overlooked. First, since vitamins were used at physiological rather than pharmacological doses and the children's nutritional status was not assessed prior to treatment, it seems likely that some improvements were due to the correction of nutritional rather than intellectual deficiencies. This is suggested by increased growth rate. More importantly, IQ tests are not designed to be dynamic measures of intellectual ability. Retesting within one year, in fact, may elevate scores due to a practice effect, even if a different test is used.

A later open trial of broad vitamin supplementation in young adults with mental retardation and Down syndrome produced no effect (Coburn 1983). High-dose vitamin therapy has been tested in a double-blind placebo-controlled trial of 56 mentally retarded children with Down syndrome and showed no demonstrable effect on several measures of intelligence (Smith et al. 1984). Kleijnen and Knipschild (1991) found no support for a direct effect of orthomolecular therapy on intelligence in a review of all published trials.

Secretin and Autism

Secretin, a gastrointestinal hormone used as a diagnostic tool in pancreatic function evaluation, was reported to have a therapeutic effect in reducing behavioral manifestations of autism in three children (Horvath et al. 1998). Following this communication, Chez et al. (2000) studied 56 children with DSM-IV diagnoses of PDD NOS or autistic disorder. Thirty-three children had a history of gastrointestinal distress. All subjects were given the CARS (Schopler et al. 1980) at baseline and postinjection of 2 IU of secretin. The authors designated a 6-point improvement in ratings as indicative of a "clinically significant" change in behavior, representing a 10–15% improvement over baseline. The CARS total scores for the entire group showed a statistically significant improvement from baseline to follow-up (Chez et al. 2000). However, when improvement was viewed in terms of clinical significance, only 13 of 56 patients demonstrated a 6-point improvement in ratings as indicative of a "clinically significant" change in behavior. Ten of these 13 responders were originally classified in the severely autistic category, a phenomenon that (as the authors point out) may be viewed as regression to the mean. A subgroup ($n = 25$) of children who had improved in the previous study were selected for a placebo-secretin crossover trial. The average CARS ratings for each group were similar regardless of the injection type, i.e., placebo or secretin. However, when administered secretin at the second injection, children were perceived by the parents as significantly improved (Chez et al. 2000). The authors concluded that overt behavioral changes did not occur following secretin injection in children with autism and that the transient im-

provement in behavioral symptoms reported by the parents could be the result of reporting bias (Chez et al. 2000).

As part of a multicenter study and using a randomized, double-blind, placebo-controlled crossover design, Owley (Owley et al. 1999) examined the efficacy of intravenous porcine secretin for the treatment of autism in 20 subjects with autistic disorder. No statistically significant difference was obtained between placebo and secretin groups in the Autism Diagnostic Observation Schedule–Generic (ADOS-G) (Lord et al. 1989) and other pertinent developmental measures at baseline and at weeks 4 and 8 (Owley et al. 1999). In summary, two controlled negative studies of secretin in autism cast doubt over its claimed efficacy. The original Horvath report awaits replication before secretin can be recommended for the treatment of autistic features.

Thyroid Hormone Treatment

Thyroid hormone and analogs have been used at physiological or supraphysiological levels for unipolar depression, bipolar affective disorder, and autism with mixed results. Experimental validation of this treatment is complicated by the immediate, stimulatory effects of iatrogenic hyperthyroid states. For this reason, evaluation of successful reports must pay particular attention to length of follow-up and appropriateness of outcome measures.

Unipolar Depression

One of the first well-controlled studies of thyroid-releasing hormone (TRH) examined its effect in nonendogenous depression (Kiely et al. 1976) and found it to be countertherapeutic. An open Japanese trial of thyroxine (T_4) in 20 adults with major depression indicated extreme variability in response, from marked improvement to mild worsening (Okuno and Nakayasu 1988). Based on these and similar studies, thyroid analogs are probably not an effective treatment for depression when prescribed alone (Stein and Avni 1988).

In contrast, triiodothyronine (T_3) effectively augmented tricyclic antidepressant response in a double-blind study of 12 cases of adult major depression (Goodwin et al. 1982). Improvement was independent of changes in plasma level of tricyclic antidepressant (mean = 252.5). Each subject had been treated with imipramine or amitriptyline for at least 3 weeks prior to addition of T_3 . In a one-month follow-up period most subjects had a statistically significant improvement on a global depression scale, although only 4 of the 12 had a change of 3 points or more, which the authors considered clinically significant (Goodwin et al. 1982). Most controlled studies of T_3 as an adjunct to tricyclic antidepressants are similarly positive (Stein and Avni 1988). In their review of thyroid hormone treatment in tricyclic nonresponders, Extein and Gold (1988) estimated that 50% of patients would improve on 25 μg of T_3 per day, a physiological dose of thyroid

hormone, not associated with serious side effects. A recent comparison indicated that T₃ may be marginally superior to T₄ for tricyclic augmentation (Joffe and Singer 1990).

Bipolar Affective Disorder

Following the publication of case series (Stancer and Persad 1982; Stein and Avni 1988), Bauer and Whybrow (1990) examined 11 subjects diagnosed with rapid-cycling bipolar disorder who received supraphysiological thyroxine in open trial and found improvement in 10. A subsequent double-blind placebo-controlled crossover study of 4 of the responders confirmed the therapeutic effect, although half of the original 10 responders relapsed eventually (Bauer and Whybrow 1990).

No comparable research data are available in youngsters, in which the use of supraphysiological doses of thyroxine probably increases the chance of undesirable side effects. This strategy cannot be currently recommended for euthyroid children and adolescents, since the effects of acute or prolonged T₃ use in this age group is unknown.

Attention-Deficit Hyperactivity Disorder

Based on observations that 48–73% of children with the syndrome of resistance to thyroid hormone (RTH) have ADHD (Weiss et al. 1997), Weiss and colleagues conducted a prospective, randomized, double-blinded, placebo-controlled, crossover study to evaluate the effect of liothyronine (L-T₃), on the behavior of 8 children with ADHD + RTH and 9 children with ADHD and normal thyroid function (ADHD only) (Weiss et al. 1997). L-T₃ had no effect on Conners Hyperactivity Index in 7 of 9 children with ADHD only. Conversely, the rating in 5 of 8 subjects with ADHD + RTH showed improvement. The authors concluded that in children with RTH and ADHD, L-T₃ in supraphysiological doses may be beneficial in reducing hyperactivity and impulsivity. In the majority of children with ADHD who did not have RTH, L-T₃ treatment had no effect (Weiss et al. 1997).

Autism

Studies of thyroid status in autistic individuals have not yielded any durable abnormalities (Abbassi et al. 1978). However, controlled trials of thyroid analogs have been conducted. Campbell and associates (1989) administered T₃ to 30 non-depressed autistic children and found no benefit compared to placebo (Campbell et al. 1989).

Down Syndrome

An increased incidence of subclinical TSH elevation and a correlation with global level of function was reported in patients with Down syndrome (Bhaumik et al. 1991). However, Tirosh and associates (1989) tested thyroid supplementation

in a group of 44 Down syndrome patients with borderline thyroid status under double-blind, placebo-controlled conditions and found no clinical benefit.

Conclusions

Several nontraditional therapeutic agents have been tried for child and adolescent psychiatric disorders. Of those that have been subjected to experimental scrutiny, only one remains promising: opiate antagonists for the treatment of hyperactivity in autistic disorder and possibly self-injurious behavior. Opiate antagonists are acceptable for limited clinical use due to their success in limited studies and the very low incidence of adverse effects. The positive results of thyroid analogs must be viewed with care. Nearly all successful trials have been carried out in severe refractory cases, and trials of thyroid analogs as a primary treatment for depression have been largely unsuccessful. Furthermore, the long-term effects of prescribing thyroid to euthyroid children and adolescents are unknown, particularly in prepubertal children.

Paradoxically, nutritional and vitamin therapies have been more passionately supported in the popular press, despite disappointing research findings. Nutritional studies have demonstrated the beneficial effect of limiting refined sugars and providing adequate morning calories on the behavior and attention of schoolchildren, but these measures should be considered matters of standard hygiene for all children. They do not comprise a treatment for any specific psychiatric disorder. Partly due to inadequate testing and partly due to lackluster results, few of these treatments have a significant place in the physician's armamentarium. The most effective nonpharmacological means of treating child and adolescent emotional illness are not simple cures, but involve comprehensive behavioral programming, social support services, and effective psychotherapy.

HERBAL MEDICATIONS AND DIETARY SUPPLEMENTS

The use of complementary and alternative medicine (CAM), such as acupuncture, herbal medications, and dietary supplements, massage therapy, and macrobiotic diets, has greatly increased over the past decade. It is estimated that between 42 and 73% of the general U.S. population uses unconventional healthcare with some frequency (Eisenberg et al. 1993, 1998; Pelletier et al. 1997). Sales of herbal preparations alone in the United States were estimated at \$3.65 billion in 1997 (Monmaney 1998) and have been reported to be growing at a rate of between 12 and 50% each year since 1991 (Mitchell et al. 1987; Cirigliano and Sun 1998; Gruenwald et al. 2000). U.S. sales of St. John's wort, for example, one of the better known herbal preparations used for treating anxiety and depression and the most commonly prescribed antidepressant in Germany (where it outsells Prozac 4:1) (O'Hara et al. 1998), were estimated at \$400 million in 1998, an increase of nearly 4000% since 1995 (Monmaney and Roan 1998).

Herbal medications have grown in popularity consonant with their increase in availability. The Dietary Supplement Health and Education Act of 1994 (DSHEA) renamed “food additives” (such as vitamins and minerals, amino acids, tissue extracts, and botanical products) as “dietary supplements,” thereby lessening their regulation by the U.S. Food and Drug Administration (FDA) (O’Reilly 1955; Slifman et al. 1998). Along with this change in nomenclature, the burden of proof has shifted from the manufacturer of the product to demonstrate safety and efficacy (as is required for drugs) to the FDA to demonstrate that the product presents a health risk (Murri 1996). To consumers, this means that herbal medications can be produced and distributed without any proof that they are safe and effective, while allowing manufacturers to make unproven claims about how their products affect the human body.

Numerous epidemiological studies have shown that unconventional therapies, including herbal medications, tend to be used disproportionately by those suffering from anxiety, depression, and chronic pain (Furnham and Smith 1988; Hollifield et al. 1990; Furnham and Bhagrath 1993; Katerndahl and Realini 1995; Vincent and Furnham 1996; Astin 1998; Davidson et al. 1998). However, there are few objective data available to demonstrate the efficacy of almost all unconventional treatments for adults, and fewer still for children and adolescents (Marwick 1995; Shaw et al. 1997; Spencer and Jonas 1997; Ernst 1998; Van Haselen and Fisher 1998; Wong et al. 1998; Eskinazi 1998). In addition, there remain no national standards for measuring competence among providers of complementary and alternative medicine (Jonas and Gold 1988; Ernst 1995; Woolf 1997). Because herbal medications and supplements are not strictly regulated by the FDA, there is little consistency among different manufacturers of these products, particularly regarding quality, dosage, and potency, which only further complicates their use. There are no assurances that a given product actually contains the active ingredients it purports to contain or that it is free from impurities (Marwick 1998). Finally, the products themselves are most often not benign, and concerns about their interactions with other drugs, supplements, and herbal medications have recently been raised (Pies 2000).

Literally hundreds, if not thousands, of herbal medications are currently marketed in the United States, and their presence is ubiquitous at every consumer level, from herbalist boutiques to grocery stores. Only those treatments that are typically employed for psychiatric purposes and have received some degree of experimental scrutiny, however, will be covered in this chapter, including St. John’s wort, ginkgo biloba, kava kava, valerian, ginseng, melatonin, S-adenosylmethionine (SAMe), inositol, and omega-3 fatty acids.

St. John’s Wort (*Hypericum perforatum*)

St. John’s wort is the name of a plant (wort in Old English) that produces bright yellow flowers on or about summer solstice, June 24, John the Baptist’s birthday.

Extracts of the plant have been used for centuries for a wide range of indications, including anxiety, depression, skin inflammation, asthma, wounds, and burns (Greenwald 1995). Over the past 10 years, numerous studies have assessed the efficacy of St. John's wort in treating a variety of psychiatric illnesses. Few of these studies, however, have met the gold standard for clinical medication trials (e.g., randomized, double-blind, placebo-controlled), and even fewer have compared St. John's wort to a control group using a standard antidepressant. In addition, no work to date has focused on children and adolescents suffering from severe depression, and long-term treatment data are not available.

Mechanism of Action

There has been much confusion about the precise active ingredient(s) responsible for the action of St. John's wort. Hypericin is now generally believed to be responsible for the clinical effects of the herb by inhibiting the reuptake of serotonin and other neurotransmitters. Hypericin extracts generally have a half-life of 24 hours and have been found to show affinity for a wide variety of neurotransmitter receptors, including adenosine, GABA_A, GABA_B, 5-HT, NMDA, and inositol triphosphate (Song et al. 1998). Though initially believed to have a weak MAO inhibitor effect, recent literature suggests that hypericin is devoid of such activity (Greenwald 1995).

Clinical Studies and Potential Indications

Linde et al.'s 1996 meta-analysis of 23 randomized trials consisting of 1757 outpatients with mild to moderately severe depression determined that St. John's wort was superior to placebo and as effective as standard antidepressants (Linde et al. 1996). The studies compared in this analysis were quite heterogeneous, as were the diagnostic criteria, compliance control, duration of treatment, and dosage regimen of St. John's wort and standard antidepressants, thereby limiting the utility of this data. Two recent reports in the *British Medical Journal* have found the efficacy of St. John's wort to be equal to that of imipramine in adults (Philipp et al. 1999; Woelk 2000), but once again limitations have made the data somewhat difficult to interpret (Spira 2001). Likewise, recent comparisons of fluoxetine and sertraline with St. John's wort, though limited in scope, strongly suggest that St. John's wort is effective in the treatment of mild to moderate depression (Laakmann et al. 1998; Brenner et al. 2000; Schrader 2000; Volz and Laux 2000). Regarding the treatment of severe depression, a recent randomized, double-blind, placebo-controlled report (Shelton et al. 2001) of 200 adult outpatients with at least a two-year history of major depression and baseline Hamilton Rating Scale for Depression (HAM-D) scores of at least (indicating severe depression) conducted at 11 academic medical centers in the United States, found no significant effect for St. John's Wort. Given the limitations of prior work, the National Institutes of Health has recently funded a multisite study comparing St. John's wort with sertraline and placebo in an 8-week trial for adults with major depressive

disorder, the results of which should be available in 2–3 years (Beaubrun and Gray 2000). In addition, other recent work has suggested that St. John's wort may have significant utility in the treatment of obsessive-compulsive disorder (Taylor et al. 1991) and premenstrual syndrome (Stevinson and Ernst 2000a). Thus, while St. John's wort appears to be efficacious, as of this writing it remains unclear whether or not it is equally as effective and safe as standard antidepressants, particularly for long-term treatment and for severe depression in adults.

To date, there are no published data of which we are aware describing the use of St. John's wort in children and adolescents. Preliminary data from an 8-week open-label clinical trial of St. John's wort in 40 youths, age 6–16 years, meeting DSM-IV criteria for major depression, have shown promising results with significant reductions in depressive symptomatology and a favorable side effect profile (Findling 2001).

Dosage and Administration

The dosing of St. John's wort is difficult to determine and has generally varied in clinical trials. Given that there is little uniformity among the different brand-name preparations available and that the amount of active product (hypericin) may vary greatly, reliable dosage strategies have yet to be devised. In general, a range of 200–1000 µg/day of hypericin is recommended for the treatment of depression (Greenwald 1995). In the United States this typically translates into 300 mg three times a day of an extract standardized to 0.3% hypericin. If there is no improvement in symptoms after 4–6 weeks, alternate treatment is advised.

Side Effects and Contraindications

Most studies have documented fewer side effects with time-limited treatment of St. John's wort than with traditional antidepressants. Still, St. John's wort falls prey to side effects typically associated with serotonin-specific antidepressants, though generally to a lesser extent. Fatigue, restlessness, and headache are perhaps the most common side effects noted, at 5, 6, and 7%, respectively, in two studies (Vorbach et al. 1997; Wheatley 1998). Gastrointestinal side effects, such as anorexia, diarrhea, nausea, and dyspepsia, have generally been reported at a lower frequency, though one study reported their occurrence at 5% (Vorbach et al. 1997). Dermatological effects have also been reported, and direct sunlight exposure has been noted on occasion to produce blisters, rash, and pruritis (Lantz et al. 1999). Though side effects have generally been described as minimal, concerns about the potential for St. John's wort to interact with other medications and herbs has received increasing attention.

St. John's wort is known to reduce the efficacy of digoxin via induction of intestinal P-glycoprotein, thereby resulting in dramatic decreases in serum digoxin levels (Cheng 2000). Concentrations of indinavir, cyclosporine, and combined oral contraceptives are also known to be decreased by concomitant administration of St. John's wort, resulting in drug resistance in HIV-positive patients,

transplant rejection, and breakthrough bleeding (with possible contraceptive failure), respectively (Bon et al. 1999; Piscitelli et al. 2000; Ruschitzka et al. 2000). St. John's wort has also been suggested as the cause of mania induction in five published cases (Nierenberg et al. 1999; Moses and Mallinger 2000) and a possible cause of cardiovascular collapse during anesthesia (Irefin and Sprung 2000). Furthermore, St. John's wort may interact with MAO inhibitors (Muller and Schafer 1996) and beta-sympathomimetic amines (e.g., ma huang or pseudoephedrine) (Miller 1998), leading to a hypertensive crisis, or serotonin-specific reuptake inhibitors (e.g., fluoxetine), leading to a serotonin syndrome (Le Bars et al. 1997).

Ginkgo (*Ginkgo biloba*)

Ginkgo, the maidenhair tree, is one of the oldest species of trees alive today, dating back 200 million years. The leaves of the tree have been valued in China for their medicinal properties for over 4000 years and have been used for a variety of indications, including asthma, vertigo, and tinnitus. More recently, ginkgo has been studied for use in dementia, intermittent claudication, and mountain sickness (O'Hara et al. 1998). Since 1994, when the German government approved a standardized form of leaf extract (EGb 761) for the treatment of dementia, the use of ginkgo has greatly increased in both Europe and the United States (Fugh-Berman and Cott 1999).

Mechanism of Action

Ginkgo extracts, particularly the flavonoids, terpenoids, and organic acids, are believed to act synergistically as free radical scavengers and antagonists of platelet-activating factor. The result of this activity is improved vascular perfusion due to dilatation of arteries and capillaries, a reduction in thrombosis, and a decrease in the release of inflammatory mediators (Walters et al. 1990b).

Clinical Studies and Potential Indications

In a randomized, double-blind, placebo-controlled study of 309 patients with Alzheimer's or multi-infarct dementia who were receiving 120 mg of EGb 761 daily, a significant improvement in cognitive function was observed (Lane-Brown 2000). The gains, though modest, were comparable to that achieved with high-dose tacrine (Fugh-Berman and Cott 1999). A number of other studies have shown similar results (Wong et al. 1998; Fugh-Berman and Cott 1999). Ginkgo may also have a role in the treatment of other psychiatric illnesses, as Kleijnen and Knipschild (1992) noted in a meta-analysis of 40 studies clinically significant improvement in adults treated with ginkgo for symptoms of anxiety, fatigue, and depressed mood. The generalizability of this data, however, may be limited as most of the studies suffered from small sample sizes, poorly defined patient populations, and nonstandardized outcome measures. To date, there are no published data describing the use of ginkgo in children and adolescents.

Dosage and Administration

Ginkgo is available in the United States in liquid or solid form for oral ingestion. Typical dosage regimens are 40 mg three times daily or 80 mg twice daily. Preparations should be standardized to contain 24% flavone and 6% terpene lactones, equivalent to the EGb 761 extract (Greenwald 1995).

Side Effects and Contraindications

Side effects of ginkgo are generally mild and include gastrointestinal upset and nausea, headache, diarrhea, anxiety, and insomnia. Though admittedly quite rare, subarachnoid hemorrhage, subdural hematomas, and intracerebral hemorrhage have all been reported in individuals receiving concurrent treatment with anticoagulant medications, likely secondary to ginkgo's effect on reducing platelet aggregation (Fugh-Berman and Cott 1999). Simultaneous treatment with anticoagulants should probably be avoided, as should treatment in individuals with impairment in blood clotting.

Kava Kava (*Piper methysticum*)

The kava plant is indigenous to Polynesia and the Pacific Islands, where it has traditionally been mixed with water and coconut milk to produce a ceremonial, tranquilizing drink. Though currently recognized for its anxiolytic and sedative properties, it has been used in the past for treating asthma, headaches, urinary tract infections, and rheumatism (Pittler and Ernst 2000).

Mechanism of Action

Kava kava is one of the few herbal medications for which the active ingredient (kavapyrones) is known. Kavapyrones comprise at least four unique substances which act as central skeletal muscle relaxants and anticonvulsants. The molecular level effects appear to be primarily due to inhibition of sodium and calcium channels, with lesser effects on the suppression of glutamate and norepinephrine reuptake. The benzodiazepine binding site is unaffected by kava kava, but the herb is believed to increase GABA_A receptor density (Beaubrun and Gray 2000).

Clinical Studies and Potential Indications

Though few studies are available, a recent systematic review and meta-analysis has confirmed the superiority of kava kava over placebo for the treatment of anxiety (Hirsch 2000). Though somewhat limited in sample size and duration of treatment, two randomized, double-blind studies have compared kava kava to benzodiazepines (oxazepam and bromazepam) with no differences noted (Greenwald 1995). At least one study has demonstrated a reduction in symptoms associated with menopause in women treated with kava kava (Fux et al. 1996).

To date there are no published data describing the use of kava kava in children and adolescents.

Dosage and Administration

Kava kava is available in a variety of oral preparations. In clinical trials, dosages have generally ranged from 100 to 200 mg of kavalactones daily either in a single dose at bedtime or in divided doses throughout the day (Greenwald 1995). Typical recommendations for store-bought preparations would be 100 mg of an extract of 70% kavalactones taken two or three times daily, equivalent to 140–210 mg of active substance per day (Hirsch 2000).

Side Effects and Contraindications

At recommended dosages, side effects have generally been confined to gastrointestinal distress, pupil dilation and blurred vision, and morning somnolence (Greenwald 1995). Kava kava has been associated with hematuria, macrocytic anemia, parkinsonism, ataxia, and severe eczema in rare circumstances and generally among those with heavy use and supernormal dosages (Suss and Lehmann 1996; Fugh-Berman and Cott 1999; Escher et al. 2001; Meseguer et al. 2002). More recently, kava kava has been implicated in 25 cases of hepatic toxicity in Germany and Switzerland, resulting in hepatitis, cirrhosis, and liver failure. In late 2001, all kava kava containing products were banned in Switzerland, and a similar proposal is under consideration in Germany (U.S. Department of Health and Human Services 2001). The use of kava kava concurrent with alcohol should be discouraged given the potentially synergistic effects. In addition, there is at least one case in the literature of a coma occurring secondary to an interaction between kava kava and alprazolam, suggesting that the use of kava kava with benzodiazepines may be contraindicated (Almeida and Grimsley 1996). Finally, the use of kava kava is discouraged in those individuals suffering from depression, as it is suggested to increase the risk of suicide (Greenwald 1995).

Valerian (*Valeriana officinalis*)

Valerian is a pink-flowered perennial, whose malodorous root has been used for centuries as a treatment for nervous conditions, insomnia, headache, stress, epilepsy, colic, and a variety of other disparate conditions (Greenwald 1995). Its use has been approved in Germany for nervousness and insomnia, and it is for these indications that it is most commonly used in the United States.

Mechanism of Action

Though numerous constituents have been identified, there is as yet no consensus as to the effective ingredient(s) in valerian. GABA_A and 5-HT_A receptor agonism, along with reuptake inhibition and decreased degradation of GABA itself, have

been suggested by animal studies as possible mechanisms of action (Walters et al. 1990b).

Clinical Studies and Potential Indications

At least two randomized, double-blind, placebo-controlled studies of valerian ($n = 27$ and $n = 128$) have found positive results for the treatment of sleep disorders in adults. In each case a standard dose of valerian (400–450 mg) was given prior to bedtime to individuals with sleep difficulties, resulting in decreased sleep latency and improved sleep quality with no sedation upon awakening (O'Hara et al. 1998). Dream recall and nocturnal awakenings were unaffected by valerian in the larger of these studies (Fugh-Berman and Cott 1999), although elsewhere it has been reported that nocturnal awakenings decrease with valerian treatment (Beaubrun and Gray 2000). While valerian appears to have some demonstrated effect, a recent review of nine randomized, double-blind, placebo-controlled trials of valerian for insomnia reported contradictory and inconsistent results among studies and recommended that a more rigorous clinical trial be performed prior to making any judgment about its efficacy (Stevinson and Ernst 2000b). To date, there are no published data describing the use of valerian in children and adolescents.

Dosage and Administration

Historically, valerian has been made into a tea by steeping 3–5 g of dried root in hot water. Valerian is currently available in capsule, tablet, liquid, and tea form. Dosages may vary, but typically 2–3 g of dried root equivalent given three times daily or at bedtime is recommended (Wong et al. 1998).

Side Effects and Contraindications

Side effects are typically rare but may include gastrointestinal disturbance, headache, poor sleep quality, contact allergies, and mydriasis (Fugh-Berman and Cott 1999). The use of other CNS depressants along with valerian may potentiate its effect.

Ginseng (*Panax* spp.)

Numerous species of ginseng exist, but only those plants within the genus *Panax* are true ginseng. Though Siberian ginseng is from the same family (Araliaceae) and is also used to decrease stress and improve endurance, it is not actually ginseng at all. Ginseng, also called the “man-root” because it looks somewhat human-like, is believed to act as a general tonic for the entire human body and is one of the most expensive herbal products available.

Mechanism of Action

While the precise mechanism of action is unclear, 25 ginsenosides, believed to be the active ingredients, have been identified to date (Greenwald 1995). Ginseng inhibits the uptake of numerous neurotransmitters, including norepinephrine,

serotonin, dopamine, glutamate, and GABA, in rat brain tissue, though it still remains unclear as to whether or not ginseng actually enters the brain (Fugh-Berman and Cott 1999).

Clinical Studies and Potential Indications

Few studies have been performed to assess the psychiatric value of ginseng. One randomized, double-blind, placebo-controlled study performed on 112 healthy volunteers age 40 and above found improvements in abstract thinking and a tendency toward faster simple reaction times with no differences in concentration, memory, or subjective experience (Greenwald 1995). In contrast, a placebo-controlled study of 60 patients on a geriatric hospital unit who took a ginseng/multivitamin preparation found no differences between the two groups in activities of daily living, cognitive function, somatic symptoms, or length of stay (Fugh-Berman and Cott 1999). To date, there are no published data describing the use of ginseng in children and adolescents.

Dosage and Administration

Capsules, tablets, and liquid are all available for oral ingestion. Dosages may vary dependent upon the desired indication. Four hundred mg daily of oral standardized ginseng was useful in improving cognitive function in the aforementioned study (Greenwald 1995).

Side Effects and Contraindications

General side effects are limited to insomnia, headache, epistaxis, anxiety, and vomiting (Panksepp and Lensing 1991). Ginseng inhibits platelet aggregation and should therefore be used with caution in individuals taking antiplatelet agents or nonsteroidal anti-inflammatory drugs (Greenwald 1995). Ginseng may act as a mild stimulant, possibly capable of potentiating the effects of MAO inhibitors, stimulants (including caffeine), and haloperidol, and should, therefore, probably be avoided in individuals using prescribed stimulants (O'Hara et al. 1998; Wong et al. 1998).

Melatonin

The precise action of melatonin is uncertain. Its synthesis and secretion from the pineal gland are controlled by the suprachiasmatic nucleus of the hypothalamus and synchronized by ambient light (Pacchierotti et al. 2000). That is, production of melatonin occurs during darkness and is inhibited during daylight. Additionally, norepinephrine stimulation is known to regulate the synthesis of melatonin from its precursor, serotonin (Pacchierotti et al. 2000).

Mechanism of Action

While the mechanism of action has yet to be clearly elucidated, this potent hormone is believed to regulate both circadian and reproductive rhythms (Pillar et

al. 1998). Similarly, melatonin itself is synthesized rhythmically, controlled primarily by the light-dark cycle. Other factors, such as genetic regulation, age, diet, and season of the year, however, have also been demonstrated to affect serum melatonin levels in humans (Pacchierotti et al. 2000).

Clinical Studies and Potential Indications

In recent years melatonin secretion has been found to be altered in numerous disorders, including migraine headaches, epilepsy, Alzheimer's disease, jet lag and other sleep disturbances, and a variety of psychiatric disorders (Pacchierotti et al. 2000). Though extensive clinical trials have not been performed, much observational and anecdotal evidence has been gathered suggesting an important, but not likely causal, role for melatonin. Pineal gland dysfunction, for example, has been hypothesized to induce the photosensitivity observed in seasonal affective disorder (Pacchierotti et al. 2000), as evidenced by the fact that melatonin administration induces a worsening of depressive symptoms (Pacchierotti et al. 2000) and that light therapy is the treatment of choice. Supersensitivity to light has also been suggested as a trait marker for bipolar affective disorder (Nurnberger et al. 1988). Significant alterations in melatonin secretion in depression have been suggested to belie the neuroendocrine axis dysfunction observed, and plasma melatonin levels have been found to inversely correlate with violent suicides (Kennedy et al. 1989). In addition, elevated levels of melatonin have been found in anorexia nervosa and in bulimics during active phases of their illness (Tortosa et al. 1989). Phase shifting and higher nocturnal levels of melatonin have been found in individuals suffering from panic disorder, and melatonin secretion has been noted to be blunted in both schizophrenia and obsessive-compulsive disorder (Pacchierotti et al. 2000).

Preliminary studies involving relatively small numbers of subjects have suggested that melatonin may be an appropriate treatment for a variety of sleep disorders, such as delayed sleep onset, fragmented sleep patterns, and phase shifting (Okumo and Nakayasu 1988; Jan et al. 1994). Children with developmental disabilities, such as blindness, deafness, mental retardation, autism, and CNS disorders, are predisposed to disturbances in their sleep-wake cycle because they often misperceive cues necessary for synchronizing their sleep with the environment (Jan and O'Donnell 1996). Melatonin has been shown to benefit over 80% of such patients in one center (Jan and O'Donnell 1996) and 68% of such patients in another (Ishizaki et al. 1999) and has been found to be highly effective in case reports of psychomotor retarded children (Pillar et al. 2000). Finally, melatonin was a successful treatment for a case of school refusal in an individual with concurrent circadian rhythm abnormalities (Tomoda et al. 1994).

Dosage and Administration

In the aforementioned studies, oral dosages of melatonin have varied from 1 to 10 mg, far in excess of that amount typically found within the human body at

any given time (300 µg). Dosages available for purchase in the United States generally range from 300 µg to 3 mg. Two types of preparations are available for purchase—natural or animal-grade preparations (including bovine pineal gland extracts) and synthetic or pharmacy-grade melatonin.

Side Effects and Contraindications

Melatonin generally appears to be safe, and tolerance has not been observed (Jan and O'Donnell 1996). The most commonly reported side effects include nightmares, headaches, morning grogginess, mild depression, and decreased libido. It has also been reported that women trying to conceive should not take melatonin, as high doses may have a contraceptive effect (Silman 1993).

Though no contraindications to the use of melatonin are found in the literature, use with sedative/hypnotics or alcohol should be discouraged given the potentially synergistic effects. Additionally, recent concerns both in the United States and abroad regarding mad cow disease and its human variant, Creutzfeld-Jakob disease, would suggest that consumption of bovine products of CNS origin may be unwise.

S-Adenosylmethionine (SAME)

SAME is synthesized from l-methionine and adenosine triphosphate (ATP) and is found in every living cell in the human body. SAME plays a critical role in the metabolic pathways of several systems, including the liver, joint cartilage, and the CNS. SAME acts as the methyl donor for a wide variety of substrates, such as lipids, proteins, hormones, and nucleic acids (Fava and Rosenbaum 1994). The first clinical trials on SAME for depression were published in 1973 (Bressa 1994).

Mechanism of Action

The precise action of SAME in the human body has yet to be elucidated. It has been hypothesized that SAME increases the fluidity of cell membranes, thereby facilitating neurotransmission by heightening the density of receptors or by increasing their efficiency (Bressa 1994). It is also known to be a beta-adrenergic and dopamine receptor agonist (Shekim et al. 1990). To date, SAME has been shown to be necessary for nerve regeneration, and limiting SAME has been shown to cause clinical sequelae such as myelopathy and depression in animal models (Cestaro 1994; Scott et al. 1994).

Clinical Studies and Potential Indications

The primary psychiatric indication for SAME to date has been for the treatment of depression. In a meta-analysis of clinical trials using parenteral or oral SAME compared to placebo and low to moderate doses of tricyclic antidepressants for the treatment of adults with depression, SAME was found to be superior to placebo and comparable to standard tricyclics (Bressa 1994). The studies referenced

in this analysis, however, were conducted between 1973 and 1992 and contained significant heterogeneity regarding their sample sizes, dosage regimens, treatment duration, and patient populations, all of which may limit the generalizability of the findings. In a randomized double-blind, placebo-controlled study of 15 adult inpatients with major depression, SAME was found to be more effective than placebo with a rapid onset of action and few side effects (Kagan et al. 1990). In a 4-week open clinical trial of adults with residual symptoms of ADHD, 75% (six of eight males) showed moderate to marked improvement with SAME (Vargas et al. 2000). To date, there is no published data describing the use of SAME in children and adolescents.

Dosage and Administration

Standard dosages for SAME have not been established. In his meta-analysis of SAME in depression, Bressa (1994) required a dosage of at least 200 mg/day by parenteral route or 1600 mg/day by oral route for inclusion in the study. He also found parenteral administration to be slightly superior to oral. Supplements marketed in the United States are for oral ingestion only and typically recommend lower dosages.

Side Effects and Contraindications

Because SAME is a naturally occurring substance, relatively few side effects have been reported in studies other than gastrointestinal distress. Of potential concern is one report of SAME-induced mania in a patient with no history of mania, arguing against the use of SAME for individuals with a history of bipolar disorder (Kagan et al. 1990). Additionally, one case of serotonin syndrome in an elderly woman taking i.m. SAME along with clomipramine has been documented (Iruela et al. 1993). The use of SAME with serotonin-type antidepressants, therefore, should be monitored closely.

Inositol

Inositol is a naturally occurring isomer of glucose, a component of lecithin and several enzymes, and is involved in the transportation and metabolism of fatty acids and cholesterol (Devlin 1992). Over the past decade, a number of small and time-limited, but well-designed treatment trials have been performed in order to discern the psychiatric effects of inositol.

Mechanism of Action

Inositol is an important precursor in the phosphatidyl-inositol second-messenger system, which is used by numerous noradrenergic, serotonergic, and cholinergic receptors (Benjamin et al. 1995a). Lithium is believed to alleviate mania by blocking the recycling and new synthesis of inositol, thereby inhibiting neurons from generating second messengers (Bersudsky et al. 1999). The novelty of inositol as a psychotropic medication lies in its action at the second-messenger intra-

cellular level, whereas conventional psychotropics act at cell membrane receptors (Benjamin et al. 1995a).

Clinical Studies and Potential Indications

While inositol blockade may decrease symptoms of mania, pharmacological doses of inositol have been shown to be effective in one double-blind, placebo-controlled study of 28 patients with major depression (Levine et al. 1995a). Though these results have yet to be replicated, a recent study of patients with bipolar depression effectively employed inositol as an add-on therapy for depressive symptoms (Chengappa et al. 2000). Three other small double-blind, placebo-controlled studies have suggested efficacy for inositol in the treatment of adults with obsessive-compulsive disorder, panic disorder, and bulimia nervosa (Benjamin et al. 1995b; Fux et al. 1996; Gelber et al. 2001). Conversely, in limited trials in Alzheimer's disease, schizophrenia, and Ect-induced cognitive impairment, inositol treatment was not found to be efficacious (Levine et al. 1995b; Barak et al. 1996; Levine 1997). We are aware of only two small studies involving children and treatment with inositol, neither of which reported significant findings. Inositol treatment showed no benefit in a study of nine autistic children or in a study of 11 children with ADHD (Levine et al. 1994, 1997).

Dosage and Administration

A therapeutic dosage has not been established for inositol. In the aforementioned studies, oral dosage has ranged from 6 to 18 g of inositol daily.

Side Effects and Contraindications

No consistent side effects or contraindications have been reported to date.

Omega-3 Fatty Acids

Omega-3 fatty acids are long-chain, polyunsaturated fatty acids from plant and marine sources. The two most commonly noted are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Preliminary studies have identified a possible role for omega-3 fatty acids in the treatment of hypertension, asthma, rheumatoid arthritis, and Crohn's disease (Freeman 2000). In addition, they may decrease risk of cardiac arrest and coronary artery disease and decrease serum triglycerides.

Mechanism of Action

Omega-3 fatty acids are thought to inhibit second-messenger systems, as high-dose therapy has been shown to suppress phosphatidylinositol-associated second-messenger activity. Omega-3 fatty acids also have demonstrated anti-inflammatory and immunosuppressive features (Freeman 2000), which may be useful in the treatment of a variety of psychiatric and nonpsychiatric illnesses.

Clinical Studies and Potential Indications

While there are reports in the literature documenting an inverse relationship between omega-3 fatty acid levels and mood disorders, schizophrenia, and dementia (Freeman 2000), causality has not been demonstrated. One small, double-blind treatment trial using omega-3 fatty acids as an adjunctive medication or as monotherapy for at least one month in patients with bipolar disorder demonstrated a significantly longer period of remission for those using omega-3 fatty acids (Freeman 2000). There are no data for use in children and adolescents, but it has been suggested that omega-3 fatty acids are safe (and necessary) in expectant and nursing mothers.

Dosage and Administration

Effective, standardized dosages have yet to be determined.

Side Effects and Contraindications

Mild gastrointestinal complaints, such as loose stools, comprise the most common side effects. Omega-3 fatty acids may also prolong bleeding time and should be used with caution in patients taking anticoagulants.

Conclusions

Countless herbal medications and dietary supplements are currently available for use in the United States for a variety of unproven psychiatric indications. While many of these products are likely to have some efficacy, the few randomized, double-blind, placebo-controlled studies that have been performed have generally contained flaws that limit the utility of their findings. In addition, almost without exception the studies have included only adult subjects, providing few data on the effects of these treatments in children and adolescents. These products are often impure, inconsistent in their potency, expensive, and rarely covered by health insurance. Making matters worse, their use is contraindicated with numerous prescribed medications.

Regardless of the fact that there is little scientific evidence to support the use of these products, consumers are using herbal medications and dietary supplements in ever-increasing numbers. A recent study of 822 children at risk for attention-deficit hyperactivity disorder found that 12% of those with a professional diagnosis of ADHD had tried complementary and alternative medicine interventions, as compared to 3% of children who did not have ADHD (Bussing et al. 2001). Although it is certainly understandable that our patients would prefer a "natural" herb or supplement to a pharmaceutically manufactured medication, it is important to remind our patients that "natural" does not necessarily mean "safe." Our experience in the United States little more than a decade ago with the amino acid l-tryptophan, which resulted in the deaths of 36 Americans and over 1500 cases of serious illness due to the eosinophilia-myalgia syndrome,

should serve as a warning to those who would blithely recommend or prescribe such treatments.

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18

Pediatric Psychopharmacology in the Consultation-Liaison Setting

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INTRODUCTION

The aim of this chapter is to present a rational approach to psychopharmacology in the physically ill child and adolescent. Psychopharmacological interventions are becoming increasingly relevant in the care of physically ill children and adolescents and are well suited to medical settings, where psychotherapeutic interventions may be difficult to implement given time constraints, the need for specially trained personnel, and the preferences of many practitioners, patients, and families for a “medical” intervention. Psychotropic medications were prescribed in 1.5% of all ambulatory medical visits for individuals 18 years and younger in 1985 (Kelleher et al. 1989), and their use in pediatric populations has continued to grow. Stimulants are the most commonly prescribed agents, followed by selective serotonin-reuptake inhibitors (SSRIs), with anticonvulsant mood stabilizers, central adrenergic agonists, antipsychotics, benzodiazepines, and lithium being prescribed in a substantial number of office visits despite most psychoactive medications being prescribed “off-label” and the existence of significant gaps in our

knowledge regarding efficacy and safety (Jensen et al. 1999). It must also be remembered that clinical trials generally enroll individuals who are free of comorbid physical disease, making psychopharmacology in the physically ill child particularly challenging and highlighting the importance of effective psychiatric consultation-liaison in medical settings and the need for a strong medical foundation in child and adolescent psychiatric training.

This chapter presents an approach to psychopharmacology in the physically ill child and should not be construed as comprehensive and all-encompassing, as the potential for specific drug-disease and drug-drug interactions is enormous and much remains to be learned. It is hoped that the current chapter will complement the information contained in the consultation-liaison chapter from the first edition of this text (Rosenberg et al. 1994). It is the reader's responsibility to determine the acceptability of any given drug or treatment according to current standards for practice. The reader is thus cautioned and advised to carefully consult the information and instructional materials in the package insert of each drug or therapeutic agent considered for clinical administration and to search other available sources in the medical and pharmaceutical literature for, among other things, any changes in indications and dosage and all warnings and precautions. This is especially important in physically ill children and when confronted with polypharmacy, new drugs, or drugs lacking approval for pediatric use.

COMORBIDITY OF PHYSICAL AND PSYCHIATRIC DISORDERS

Descriptive epidemiological studies have provided convergent evidence that physical and mental health are related (Dew 1998), but the nature of this relationship remains poorly understood. Despite a growing awareness that the traditional dichotomy between physical and mental health is at base a false dichotomy (Detre 1987), some degree of dualistic thinking remains a practical reality in the clinical practice of medicine. Physical and psychiatric disorders thus may appear to be associated in a variety of ways, but definitive judgments regarding causality are often elusive given the complicated nature of reality. Unidirectional causal models appear to be overly simplistic, but it is generally acknowledged that psychiatric symptomatology may develop in the wake of physical disease and/or in association with the use of particular medications. Nevertheless, the possibility that psychiatric symptoms in a child may be explained wholly or in part as a consequence of physical disease, a drug, or a toxin should always be considered, highlighting the importance of medical differential diagnosis in the evaluation of psychiatric symptoms (Campo 1993). A comprehensive review of the physical causes of common psychiatric symptoms and disorders in children and adolescents is beyond the scope of this chapter, but physical disorder may be judged to cause or predispose to psychiatric disorder by virtue of the biology of the

disease process and/or by virtue of the stress and environmental disruption associated with the experience of physical illness. The converse, the potential impact of psychiatric disorder on the development and course of physical disease, has not been well studied, but is nevertheless a topic of increasing relevance given the possibility that psychiatric disorder might have a negative impact on the course and even the pathophysiology of physical disease (Friedman et al. 1995). Physical and psychiatric comorbidity might also be reflective of a shared pathophysiological process or of shared vulnerability factors in specific physical disorders such as migraine, which has been strongly associated with both anxiety and depression and sometimes treated with antidepressant medications (Merikangas and Stevens 1997). Another interesting example is the description of a shared genetic vulnerability to atopy and internalizing psychiatric symptoms (Wamboldt et al. 1998).

Chronic physical illness in children and adolescents has become an increasingly common focus of attention in pediatric medicine. Most physically ill children survive into adulthood given improvements in pediatric health care, with chronic physical illness affecting 10–12% of children in the United States and approximately 25% of this group suffering from significant functional impairment in association with their disease (Gortmaker et al. 1990). Physically ill children have been found to be at greater risk of suffering from psychiatric symptoms and disorders than physically healthy peers independent of sociodemographic factors in both community-based and clinical samples (Gortmaker et al. 1990; Rutter et al. 1990). Though most studies of the relationship between psychiatric disorder and chronic physical illness have been cross-sectional, the development implications of pediatric physical illness may be considerable, with a longitudinal study of juvenile diabetes mellitus identifying psychiatric disorder in nearly half of affected individuals by age 20 (Kovacs et al. 1997). Physically ill adults also appear to be at greater risk of psychiatric disorder, with a global odds ratio of 2–3 and the risk of psychiatric disorder increasing as one moves from general population samples, to primary care, and on to specialty care (Dew 1998). The observed increase in risk is likely multidetermined, with the specific type of physical disorder, exposure to somatic treatments such as radiation and medications, personal and family history of psychiatric disorder, coping variables, social support, and associated life events and stressors all potentially playing a role (Dew 1998).

While there certainly appear to be psychosocial stresses common to the experience of chronic illness in childhood regardless of type, the strength of the association between physical illness and psychiatric disorder appears to vary depending on the specific type of physical disorder, with the greatest risk for psychiatric disorder being associated with physical disorders involving the brain (Breslau 1990; Rutter et al. 1970). In the Isle of Wight Study, psychiatric disorder was noted in 7% of physically healthy children, 12% of those with nonneurologi-

cal illness, and 34% of those with a brain-related disorder such as epilepsy or cerebral palsy with the presence of a structural brain abnormality increasing risk even further (Rutter et al. 1970). Psychiatric disorder is also quite prevalent in children with a history of traumatic brain injury (TBI) (Max et al. 1998). Individual differences in risk for psychiatric disorder may be independent of physical health, but unique vulnerabilities to psychiatric disorder may only become relevant in the context of physical illness. For example, premorbid individual and/or family history of psychiatric disorder may become relevant for a particular individual only in association with physical disease or the use of a specific medication. A history of maternal depression increases the risk for depression in youth with diabetes (Kovacs et al. 1997), and a family history of depression increases the risk of developing depression in epileptic youngsters treated with phenobarbital (Brent et al. 1987).

The potential impact of psychiatric disorder on physical health and well-being is especially important to consider given the potential benefits that may be associated with psychopharmacological interventions. (1) Psychiatric disorder may present with physical symptoms or distress. Medically unexplained physical symptoms, particularly recurrent complaints of pain, may be among the most common ways for psychiatric disorder to present in pediatric primary care and have been associated with an increased risk for psychopathology, functional impairment, perceived health related impairment, and overuse of health and mental health services (Campo et al. 1999). (2) Symptoms of psychiatric disorder may be misinterpreted as signs of physical disease, as in the example of an asthmatic patient with comorbid panic anxiety who misattributes symptoms of shortness of breath, lightheadedness, and palpitations as being due to bronchoconstriction and hypoxia and initiates aggressive treatment with beta-sympathomimetic agonists (Baron and Marcotte 1994). Such misattributions have the potential to result in a vicious cycle where treatment of presumed asthma can worsen comorbid anxiety. (3) Psychiatric disorder may also play a role in precipitating or exacerbating the course of preexisting physical disorder and may contribute to real or perceived functional impairment associated with the physical disorder (Friedman et al. 1995). Consequently, active psychiatric treatment has the potential to improve both physical health and perceived quality of life (Lamberg 1996). Conversely, psychiatric disorder may have direct effects on the pathophysiology of physical disease. Continuing with the example of asthma, there is evidence that the hyperventilation and autonomic arousal associated with panic anxiety may actually precipitate bronchoconstriction in vulnerable individuals (Smoller et al. 1999). Another example is provided by findings that depression in diabetic youth has been associated with an increased risk for the later development of retinopathy, even when an effort is made to control for the impact of metabolic status (Kovacs et al. 1995). (4) Finally, psychiatric disorder can have negative effects

on adherence to medical regimens and lifestyle, as in the case of the depressed adolescent with asthma who skips medication doses, fails to participate in symptom monitoring, gains weight due to associated hyperphagia and dietary indiscretion, and smokes cigarettes. A recent meta-analysis of the adult literature suggests that comorbid depression increases the risk of nonadherence to medical regimens by a factor of three and is likely a risk factor for poor outcomes in the medically ill, while anxiety had variable and nonsignificant effects (DiMatteo et al. 2000).

CONSULTATION AND ASSESSMENT

Pediatric psychiatric consultation may be requested for a variety of indications, including emergencies such as agitation or delirium, help in exploring the relationship between recognized physical disease and associated psychiatric symptoms, the management of psychiatric disorder in medically ill children, and the assessment and management of presumably medically unexplained physical symptoms or somatization (Kush and Campo 1998). Despite a growing knowledge base regarding the interrelationship between physical and mental health, psychosocial services for physically ill children are limited, referral rates to mental health services are low, and available services are fragmented (Sabbeth and Stein 1990). The effective consultant must recognize that initial intake is a critical time and must determine the core reason for consultation and whether the referring professional considers the request to be emergent or routine. An effort should be made to call or speak directly with the referring physician or service in order to clarify the ostensible reason for consultation, obtain key patient-focused information and insights, and ensure that the patient and family are aware of the consultation request and agreeable with proceeding. In inpatient settings it is also advisable to clarify that the appropriate consultation request has been written in the medical record.

Successful consultation is rooted in respect for patients and families. It is essential to remember the importance of confidentiality and the need to respect patient privacy, even on a busy hospital ward. An effort to clarify the understanding of the patient and family regarding the reason for consultation is generally helpful, as is time spent explaining the consultant role. It is also important for the consultant to appreciate and evaluate the power and potential impact of stigma for any given patient, family, and referral source. Children with physical illness, their families, and their medical caretakers may at times be exquisitely sensitive to the involvement of a psychiatric consultant, as it may be perceived to imply that they are somehow “not coping well” with the physical disease. The focus provided by the medical setting can nevertheless present advantages to the consultant in that many patients and families who would otherwise be unwilling to consider evaluation or treatment for a “mental” disorder may be willing to pro-

ceed if psychiatric consultation is practically framed as an accepted component of traditional medical care and geared toward improving physical health, functional status, and well-being.

Careful assessment is the foundation on which subsequent intervention can be built, and the temptation to intervene quickly must be tempered by an understanding that careful diagnosis precedes treatment. Perhaps more than anything else, careful assessment is essential to the therapeutic alliance and establishing a partnership with the patient and family. Relevant medical records, including any available psychiatric records, should be reviewed carefully beforehand if possible. Optimal consultation requires a willingness to obtain information from multiple sources, including the patient, parents, caretakers, extended family members, the school, outside agencies, and other treating professionals, such as the primary care or specialty physician and the primary nurse. Information from outside sources must be obtained with permission, except in emergent circumstances. Developmental issues are also important to consider from the perspective of disease management. For example, parental involvement in disease management should evolve over the course of a disease (e.g., a 12-year-old should not be considered capable of managing a chronic illness alone, yet should be moving along a developmental path toward greater self-sufficiency). Patient and family strengths should be recognized, as should health-promoting behaviors such as maintaining positive peer relationships, socialization, and exercise.

The potential impact of physical factors on target symptoms must be considered. Relevant issues include the impact of any recognized physical disorder, the possibility of an unrecognized physical disorder, and the impact of medications or other treatments on observed psychiatric symptomatology. The relative contributions of one physical factor or another are most often difficult if not impossible to establish, with psychiatric symptoms often appearing to be multiterminated, even when physical factors are likely involved. Current and past medical history, especially any history of central nervous system illness such as epilepsy or traumatic brain injury, should be carefully explored and the possibility of unrecognized physical factors impacting on the patient's symptoms considered. Drugs are frequently implicated as potential physical causes of psychiatric symptoms, though a causal connection is often difficult to establish and available information is often based on anecdote and case reports (Medical Letter 1998). Current medications, including use of contraceptives, vitamins, dietary supplements, and herbal remedies, should be determined. Consult the package insert, other print resources such as the *Medical Letter*, internet search services, and/or local pharmacology resources regarding the potential psychiatric effects of current medications (Strain et al. 1998). Additional considerations should include substance abuse/withdrawal and toxin exposure, including inadvertent exposures such as lead or exposure consequent to substance use as with hydrocarbon inhalants. It is also especially important to consider the possibility of pregnancy in

females given the potential for pregnancy to impact mood, behavior, and any ongoing disease process such as metabolic control in diabetes.

The consultant must feel comfortable that adequate physical assessment has taken place and should not hesitate to perform a physical examination, suggest additional diagnostic testing, or recommend additional medical consultation when relevant. The fact that a particular patient has been under a physician's care and "medically cleared" for psychiatric consultation is no excuse for intellectual laziness and does not guarantee that serious physical factors relevant to the presentation have not been overlooked. Aside from the clinical syndrome of delirium (see below)—an especially important clue to the presence of serious physical disorder—the phenomenology of psychiatric symptoms generally provides little clue to whether a physical etiology is operative, and the absence of delirium does not ensure physical health. Similarly, the association of emotional or behavioral symptoms with psychosocial stress is hardly proof of psychological origin.

When a potential physical cause of psychiatric symptoms is identified, a judgment needs to be made as to whether efforts to treat the primary physical disorder or modify potentially noxious associated treatments are justified. For example, consideration might be given to withdrawing a medication thought likely to be responsible for target psychiatric symptoms providing that discontinuing the medication was medically feasible. There are numerous situations, however, where a particular medication may be negatively impacting a given patient's psychiatric status but discontinuing the medication is not a reasonable option. An example might include the use of a selective immunosuppressant such as tacrolimus in organ transplantation where other agents have proven ineffective in preventing rejection. In such cases, proceeding with standard psychopharmacological and psychiatric interventions for the recognized psychiatric symptoms may be reasonable regardless of the presumed etiology.

The characteristics, course, and context of the patient's psychiatric symptomatology must be assessed and documented, and the examiner must carefully assess the mental status, with special attention to the possibility of delirium in the medically ill. Potential target symptoms for subsequent intervention should be identified and a baseline established, including a baseline appreciation of the patient's functional status. In addition to more typical social and family assessment, an additional element may include the assessment of the patient's and the family's relationships with the medical caretakers. The importance of clear, concise, and effective communication with patients, families, and colleagues cannot be overemphasized. Psychiatric disorders may be underdiagnosed in the physically ill due to the perception that the emotional or behavioral symptoms are "understandable reactions to stress" or are purely the consequence of physical disease and cannot be "counted" as symptoms necessary to the diagnosis of a psychiatric disorder. An "inclusive approach" would consider all symptoms of depression noted on examination to be relevant to the diagnosis of depression

regardless of whether physical illness could be responsible. One argument for such an approach is that decisions to exclude particular symptoms from consideration in the psychiatric diagnostic process can be quite subjective, which could increase specificity at the expense of sensitivity and sacrifice reliability (Fulop and Strain 1991).

Assessing the need for disease-specific education can be critical, and the consultant should not assume that the child and family understand the fundamentals of the child's physical illness. In this respect, it may be necessary for the consultant to seek additional information and education about the patient's disease and the specifics of its management.

PRINCIPLES OF PSYCHOPHARMACOLOGICAL MANAGEMENT IN THE PHYSICALLY ILL CHILD

There is a paucity of research regarding psychopharmacological interventions in physically ill children and adolescents, although clinical experience and available evidence in the adult literature suggest that psychopharmacology could hold considerable promise in this population. Specific areas for consideration include the use of psychotropics to treat comorbid psychiatric disorder in the physically ill, in pain management, in the management of delirium and agitation, and as adjunctive agents for a variety of symptom complexes associated with physical disease such as the management of narcotic induced sedation. The approach outlined below assumes a working diagnostic formulation and the identification of target symptoms potentially amenable to psychopharmacological strategies. The safety or efficacy of a particular drug in a specific patient is never certain, making it essential to individualize clinical treatment in any potential therapeutic encounter (Nies and Spielberg 1996). The reader is reminded that the examples provided below are primarily illustrative and not comprehensive in nature and is encouraged to consult available resources regarding the potential impact of psychopharmacological intervention in particular physical disorders and in conjunction with coadministered medications. The absence of reports of adverse reactions in the literature does not provide definitive assurance that such reactions are not possible, making caution advisable.

Education

Communicating the belief that the child's illness is a challenge to be managed and overcome can be helpful in directing the patient and family to a more rehabilitative mindset, encouraging active coping with illness rather than passive acceptance. It is helpful to devote time and attention to the education of the patient, family members, and relevant involved professionals regarding the psychiatric diagnosis and reasonable treatment options within the context of the patient's

physical illness. The diagnostic impression should be discussed clearly and frankly, as should relevant areas of uncertainty. Information should be presented with the goal of shared decision making and true informed consent. Children are rarely self-referred, but they benefit from being treated as partners in their own care providing that the involved adults employ reasonable developmental expectations and common sense. An exploration of available treatment options should address potential risks and benefits, including what is known and not known about psychopharmacological interventions in the circumstance presented. The potential risks and benefits of no intervention should also be explored in keeping with available knowledge. Educational efforts create important opportunities for the clinician to explore patient and family concerns and beliefs regarding the use of psychoactive medication and prior experiences with such agents. The subjective meaning of psychoactive medication use in general and of specific agents can sometimes prove to be quite important for the clinician to understand.

Efforts to encourage and assist self-education efforts by patients and families can also be worthwhile, and helpful publications regarding psychiatric medication use in children have become increasingly available (Dulcan 1999; Wilens 1999). The name, dosing, administration schedule, monitoring, potential side effects, potential drug interactions, cautions, and cost of recommended medications should be discussed as appropriate to the clinical situation. Treatment expectations and the time frame necessary to assess efficacy should also be reviewed. Physicians should ideally provide information and informed advice, but in the end it is the patient and family who ultimately decide upon the preferred course of action. However, while physician flexibility and openness to patient and family preferences are important, the physician should resist and avoid colluding with unreasonable or potentially harmful choices by patients and families.

Considerations in Selecting a Medication

Considerations in the choice of a psychopharmacological agent in the pediatric medical setting best follow the general recommendations suggested by Preskorn (1999) and include primary considerations of safety, tolerability, efficacy, cost, and simplicity. Safety is generally the foremost consideration in pediatric psychopharmacology and takes on special significance in physically ill children, who may be at greater risk of treatment complications and side effects. It is important to remember that no drug produces a single effect. The therapeutic index of a given drug reflects the ratio of the median toxic dose to the median effective dose of the drug and provides a relative estimate of safety when a drug is used for a specific indication. Drugs with a wide therapeutic index tend to be safe within a relatively broad range of doses at or beyond those therapeutically recommended, while drugs with a narrow therapeutic index may become effective only at doses relatively close to the potentially toxic range. The acute and short-term

safety profiles of many commonly used psychoactive agents have been inadequately studied, and little or nothing is known about the long-term safety of pediatric psychopharmacological agents (Jensen et al. 1999). A healthy respect for uncharted territory is warranted, particularly in physically ill children where our ignorance is even greater. Tolerability may be an especially important issue in the physically ill, where the overall burden of discomfort, distress, and “hassle” can be considerable. The more sites of action of a drug, the greater the number of potential adverse effects it can produce, making drugs with multiple modes of action potentially more complex to manage in the physically ill. Tolerability problems can develop acutely, but can also develop over time with long-term use. Efficacy is the point of psychopharmacological intervention, and while concerns about efficacy are not unique to medical settings, they are no less relevant. Knowledge of the efficacy of psychoactive medications for the treatment of specific psychiatric disorders in physically ill children and adolescents is sorely limited and based almost completely on clinical experience and extrapolation from studies in adults. The impact of treatment with a specific drug for a child with a specific physical condition may thus be difficult to anticipate given the relative lack of published literature. Aspects of efficacy such as speed of response can be quite important clinically, particularly in the agitated and delirious patient or in other situations where psychiatric disorder appears to negatively influence physical health and recovery. In addition, while the maintenance and prophylactic efficacy of intervention can be particularly relevant in the physically ill, data-based guidance is lacking. Simplicity of drug regimen is of special importance in the physically ill. Physically ill children often take multiple other medications and struggle with a variety of demands and restrictions related to the physical illness proper. These all have the potential to serve as distractions to compliance with the psychiatric regimen and increase the chance of medication errors. Ease of clinician use is another important aspect of simplicity of drug regimen since many physically ill children rely on nonpsychiatric physicians for their psychopharmacological management. The “ideal” psychoactive medication would thus have little need for dose titration (i.e., can be started at or close to an effective dose), with an easily determined optimum dose, once-daily oral administration, and no special need for laboratory testing to guard against toxicity or determine a therapeutic window (Preskorn 1999).

Some understanding of basic pharmacological principles is necessary in assessing the potential safety and suitability of the drug being considered (see Chapter 5). Pharmacodynamics is concerned with mechanisms of drug action and the biochemical and physiological effects of drugs; pharmacodynamics is concerned essentially with effects at receptors or biologically active sites and with what the drug does to the body (Benet 1996). Pharmacokinetics deals with the absorption, distribution, biotransformation, and excretion of drugs and focuses on how the body handles a drug (Benet 1996). Pharmacokinetic factors

and dosage are the critical factors in determining drug concentration at the relevant sites of pharmacodynamic action over time.

Important issues relevant to psychopharmacological intervention in the physically ill child are discussed in the following sections.

Drug-Disease Interactions/Physical Comorbidity

Physical disease can modify drug action via alterations in the absorption, distribution, metabolism, and elimination of specific psychopharmacological agents. Drug absorption may be influenced by factors such as gastrointestinal disease, changes in gut motility, hepatic portal hypertension, or by the coadministration of other drugs, foods, or substances. Factors such as degree of drug protein binding, drug solubility, physical disease, and nutritional status can also influence a given drug's volume of distribution. Ascites and edema associated with specific disease states may increase the volume of distribution for water-soluble or protein-bound drugs, while dehydration and wasting may reduce volume of distribution (Rubey and Lydiard 1999). The enzyme systems involved in drug metabolism or biotransformation are primarily located in the liver. Additional metabolic capability can be localized in the kidneys, gastrointestinal tract, and lungs. The lipophilic nature of most psychoactive drugs that facilitates passage through biological membranes and access to primary site of action may hinder elimination from the body. Biotransformation generally involves conversion of these relatively lipophilic substances into more water-soluble metabolites, usually with some loss of pharmacological activity. Drug excretion then generally takes place in the urine or bile, most often after some type of biotransformation has taken place.

End organ failure or disease is not necessarily a contraindication for the use of most psychopharmacological agents, although careful monitoring and a willingness to modify drug dose or administration schedule may be necessary. Conversely, the use of a particular psychopharmacological agent may impact the pathophysiology of the disease process both positively and negatively, and such interactions should be anticipated when possible based on available knowledge. Choice of a particular psychopharmacological agent may properly be influenced by the potential effects on the comorbid physical disorder, providing that the chosen psychoactive drug is potentially efficacious. For example, one might be concerned about potential effects on seizure threshold with comorbid epilepsy, on respiratory drive and airway resistance with cystic fibrosis or asthma, on glycemic control in diabetes mellitus, or on heart rate, blood pressure, and cardiac conduction with comorbid cardiovascular disease. Nonspecific physical symptoms commonly associated with chronic illness may also be important and capable of influence. For example, a depressed child with a chronic debilitating illness associated with poor weight gain might benefit from a trial of a novel antidepressant like mirtazapine given the commonly reported side effect of increased appetite and weight gain, just

as a child suffering from nausea might benefit from the drug's ability to block 5-HT₃ receptors (Buck 2000). Some specific examples of how physical disorders and psychopharmacological interventions may interact follow.

Hepatic disease. Drug metabolism in the liver can be affected by changes in enzyme induction or inhibition as well as by changes in hepatic blood flow. Hepatic disease can lead to reduced first-pass extraction and biotransformation of psychoactive drugs. Liver failure has the potential to result in higher drug plasma levels after oral administration, increased risk of toxicity in drugs with a narrow therapeutic index like the TCAs, and an increased risk of side effects. Most psychoactive drugs, with the notable exceptions of lithium and gabapentin, are primarily metabolized in the liver. Gabapentin is excreted essentially unchanged by the kidney and has no appreciable protein binding. Liver disease may also have effects on volume of drug distribution via reductions in hepatic protein production, which can increase the availability of free drug for highly protein bound drugs such as most of the antidepressants, diazepam, and haloperidol, potentially increasing the risk for toxicity despite expected plasma levels. Drugs with minimal protein binding include lithium, gabapentin, and venlafaxine.

Dose reductions are generally recommended for most psychoactive medications in severe hepatic disease, with a general rule of thumb being to begin with a 25–50% reduction from the usual dose, then adjusting accordingly (Rubey and Lydiard 1999). Of the SSRIs, citalopram and fluvoxamine are slightly less highly protein bound, and paroxetine has no active hepatic metabolites, giving perhaps a slight edge to these agents in liver disease. Nefazodone is highly protein bound and subject to high first-pass metabolism; though less highly protein bound, some dose reduction is also suggested with venlafaxine (Rubey and Lydiard 1999). Of the benzodiazepines, lorazepam, oxazepam, and temazepam do not undergo oxidative metabolism in the liver and are probably the least affected by liver disease and the safest to use, since oxidative metabolism appears to be affected earliest and most severely in liver disease (Collis and Lloyd 1992).

Some psychopharmacological agents such as carbamazepine, valproate, nefazodone or phenothiazines such as chlorpromazine are potentially hepatotoxic and thus should be avoided or used only with caution in the presence of hepatic disease. Chlorpromazine and related antipsychotics have been associated with cholestatic jaundice, possibly secondary to a hypersensitivity reaction in predisposed individuals. Mild nonprogressive elevations in transaminases have been reported with olanzapine (Cadario 2000) and are not unusual with the use of carbamazepine or valproate, but more serious idiosyncratic hepatitis and potentially fatal hepatotoxicity can also occur in conjunction with use of carbamazepine and valproate. No cases of fatal hepatotoxicity due to valproate alone have been reported in individuals older than 10 years of age. The use of the long-

acting stimulant pemoline has also been associated with potentially fatal hepatotoxicity (Rosh et al. 1998).

Renal Disease. Not all psychoactive drugs have been adequately evaluated in renal failure. With the most notable exceptions of lithium and gabapentin, mild to moderate impairments in renal function generally do not prompt routine changes in drug dosage or administration, though an individualized approach to the patient is most optimal. Drug absorption may be diminished due to gastric alkalization, and volume of distribution can be affected by ascites and edema for more water-soluble compounds. Reductions in albumin may lead to decreased protein binding of medications, potentially making patients with renal disease more vulnerable to medication side effects or toxicity despite expected serum levels. Renal elimination of a drug may be affected by alterations in renal blood flow, active tubular secretion, or passive tubular reabsorption (Kalash 1998). Lithium is the psychotropic agent most likely to be affected by changes in renal function, as it is excreted essentially unchanged in the urine. Because of its small molecular size, lithium is completely dialyzed. It is most often given as a single dose immediately after dialysis, and levels need to be monitored carefully; dosing may not be necessary until the next dialysis. Since most psychoactive drugs are primarily dependent on hepatic metabolism, dosage adjustments are usually unnecessary in the face of mild to moderate impairments in renal function, but it must be remembered that clinically significant metabolites of specific psychoactive agents may accumulate in end-stage renal disease. In such circumstances, increases in administration interval and possible dose reduction should be contemplated. Renal clearance is important for clonidine, as well as for many of the active and inactive metabolites of TCAs and benzodiazepines. Paroxetine and venlafaxine levels may increase in moderate renal failure, and dose adjustments may be needed (Rubey and Lydiard 1999).

Lithium adversely affects renal tubular function and has been associated with decreased renal concentration ability and nephrogenic diabetes insipidus; while this effect is likely to be reversible early in the course of treatment, it may become irreversible over time (Gitlin 1999). While the renal effects of lithium are generally benign in the absence of toxic levels, interstitial nephritis and renal failure may develop in a small minority of patients (Dunner 2000).

Gastrointestinal Disease. Gastrointestinal mucosal integrity and motility can affect the rate and degree of orally administered drug absorption (Leipzig 1990). Many psychoactive drugs are weak bases and become ionized in the acidic environment of the stomach, thus limiting absorption until emptied into the more alkaline environment of the small intestine. Delayed gastric emptying as in gastroparesis can slow absorption, and disease of the small intestine such as Crohn's disease or celiac disease and short-gut can also reduce drug absorption, although

other aspects of the disease process such as effects on protein binding and volume of distribution can have contrary effects. Increases in intestinal transit as in diarrheal illness or gastroenteritis can also limit the absorption of drugs such as lithium (Leipzig 1990).

The relationship between gut and brain is complex, with the gut employing neurotransmitters such as serotonin and being the only organ system that contains an intrinsic nervous system capable of mediating reflexes without input from brain or spinal cord (Gershon 1998). Reciprocal interactions between gut and brain certainly appear to be plausible and raise questions as to whether treatment for psychiatric disorder in patients with gastrointestinal disease might benefit the physical disease process and vice versa. For example, the active treatment of depression might have a positive impact on the course of disease in inflammatory bowel disease (IBD) (Kast 1998), and the presence of psychiatric disorder appears to alter the perception of disease severity in IBD and is associated with greater functional disability (Walker et al. 1996).

Cardiovascular Disease. Significant cardiac disease can reduce drug clearance by reducing perfusion of the liver and kidneys, and volume of distribution for drugs may increase with congestive heart failure and associated fluid retention (Rubey and Lydiard 1999). Conversely, psychopharmacological agents may have effects on cardiovascular function. TCAs can be deadly in overdose and have been associated at therapeutic doses with increased heart rate and increased blood pressure in children, as well as cardiac conduction disturbances and a possible risk of sudden death (Werry et al. 1995; Wilens et al. 1996; Varley and McClellan 1997). TCAs have class I antiarrhythmic or quinidine-like properties and may be more dangerous in patients with preexisting cardiac disease (Glassman 1998). At therapeutic doses, SSRIs have been associated with a modest slowing of heart rate, but generally do not influence resting or postural blood pressure or cardiac conduction, though severe sinus bradycardia has been reported rarely in adults (Settle 1998). Both bupropion and venlafaxine has been associated with increases in blood pressure in studies of adults, but cardiovascular effects have not been well studied in children (Glassman 1998). Lithium has uncommonly been associated with adverse cardiovascular effects such as sinus node dysfunction, arrhythmia, and syncope, although the more common electrocardiographic findings of T-wave flattening and inversion are generally considered to be benign (Dunner 2000).

Clonidine can decrease systolic blood pressure and reduce cardiac output and heart rate, but clinically significant hypotension or orthostasis is unusual (Hunt et al. 1990). Cardiac arrhythmias have been reported, as has sudden death when clonidine was used in combination with methylphenidate, raising concerns about the routine use of clonidine in the presence of cardiovascular disease and

suggesting the need for careful monitoring of the EKG and clinical vigilance (Cantwell et al. 1997).

Antipsychotic medications may also have cardiovascular effects. Clozapine has been associated with tachycardia, hypotension, and hypertension (Miller 2000). Low-potency antipsychotics such as chlorpromazine, thioridazine, and clozapine tend to have the most anticholinergic, antihistaminic, and α -adrenergic blocking effects, making hypotension a special concern. These agents may also have quinidine-like effects on cardiac conduction and may cause QT prolongation, which has been noted with thioridazine and also with the atypical agent risperidone (Alpert et al. 1997; Yap and Camm 2000). High-potency agents such as haloperidol, usually in higher doses and when administered parenterally in critically ill patients, have also been associated with lengthening of the QT interval and torsades de pointes or multifocal ventricular tachycardia, which has the potential to progress to ventricular fibrillation and sudden death (Sharma et al. 1998). Pimozide may also inhibit cardiac conduction due to calcium channel blocking activity, and its use with calcium channel blockers such as nifedipine is to be avoided (Alpert et al. 1997).

Pulmonary Disease Respiratory problems can impact upon drug handling. Both hypoxia and hypercarbia can impact on the pharmacokinetics of psychoactive medications. Changes in serum pH can alter the amount of free drug available at the site of action and can also impact drug absorption and distribution (Rubey and Lydiard 1999). It is worth remembering that a serious chronic disease like cystic fibrosis, ostensibly a pulmonary disease, can have broad systemic effects despite unavoidable conceptual associations with a single organ system. For example, individuals with cystic fibrosis may be less efficient in handling lithium as a consequence of the core genetic defect, which affects ion channels involved in electrolyte transport, making some degree of caution appropriate in lithium dosing in patients with cystic fibrosis (Brager et al. 1996). Also of note is the finding that the clearance of agents that undergo conjugation such as lorazepam may actually be increased in cystic fibrosis (Kearns et al. 1996).

The relationship between anxiety and respiration has generated considerable interest. Hypersensitivity to respiratory phenomena such as increased carbon dioxide levels is proposed to be involved in the pathogenesis of panic anxiety (Klein 1993). Similarly, cognitive hypersensitivity to anxiety-related bodily sensations has also been proposed as the source of the "false alarm" that triggers panic (Smoller and Otto 1998). Anxiety has been commonly associated with asthma, with asthmatic children in one study being twice as likely as controls to experience an anxiety disorder (Bussing et al. 1996) and atopic disorders and internalizing disorders appearing to share a common genetic vulnerability (Wamboldt et al. 1998). Interestingly, however, there does not appear to be a correlation

between asthma severity and anxiety (Wamboldt et al. 1998). Panic and associated hyperventilation also have the potential to trigger or exacerbate asthma via airway cooling or vagally mediated bronchoconstriction (Smoller et al. 1999). Consequently, active intervention for anxiety may be particularly important in children with asthma or other respiratory diseases, but there is little research available to guide practice. Vocal cord dysfunction, a condition often confused with asthma, is also commonly associated with anxiety symptoms and disorders in affected children (Gavin et al. 1998).

While benzodiazepines are appealing in the acute treatment of anxiety given a history of efficacy and relatively rapid onset of action, there has been considerable debate regarding their use in the treatment of patients potentially vulnerable to respiratory depression. Benzodiazepines can suppress respiratory drive and exacerbate hypercapnia in vulnerable patients, but with close monitoring and cautious dosing safe and effective use appears possible (Smoller et al. 1999). Active treatment of anxiety and agitation can prove beneficial in the intensive care setting, where the judicious use of anxiolytics can prove helpful in the mechanically ventilated patient and may even be of benefit in efforts to wean selected patients from mechanical ventilation. The intermediate half-life benzodiazepine lorazepam may be preferred given a reduced likelihood of accumulation and some evidence suggesting that it may be less likely to induce respiratory depression than diazepam (Denault et al. 1975). Benzodiazepines are most hazardous at higher doses or when used parenterally or in combination with other drugs that may depress respiratory drive such as opiates. It should also be noted that epidemiological studies have reported an increased risk of death in asthmatic patients taking antipsychotic or sedative drugs, and while noncausal mechanisms such as nonadherence are of likely importance, causal mechanisms such as decreased respiratory drive have also been suggested (Joseph 1997).

Serotonin appears to be involved in modulating central control of respiration, and tryptophan depletion may produce hyperventilation (Kent et al. 1996). The SSRIs and newer antidepressants such as nefazodone and venlafaxine may be especially useful in the treatment of anxiety and depression associated with comorbid respiratory disease, and SSRIs have been reported to reduce sensitivity to carbon dioxide and block associated panic attacks (Kovacs et al. 1995). Buspirone may also be worthy of consideration in the treatment of generalized anxiety associated with pulmonary disease given its relative safety and tolerability, lack of respiratory depression, and even mild respiratory stimulant effects (Craven and Sutherland 1991). No respiratory depressant effects have been associated with the use of SSRIs, buspirone, TCAs, bupropion, venlafaxine, or nefazodone (Rubey and Lydiard 1999). Caution regarding the use of TCAs in asthmatic children has been suggested due to serious side effects in one small study (Kanner et al. 1989), although a subsequent case series and review reported the medications to be somewhat better tolerated despite a variety of adverse reactions in a

minority of patients (Wamboldt et al. 1997). Though there has been speculation that clonidine might have effects on airway resistance in asthma, one small study found no significant effects on airway reactivity (Foxworth et al. 1995).

Neurological Disorders and Epilepsy The high rates of comorbid psychiatric disorders observed in youth with epilepsy often necessitates the use of psychotropic medication, which paradoxically can have the potential to lower seizure threshold directly or interfere with the pharmacokinetics of the anticonvulsant regimen. A variety of anticonvulsants have been associated with psychiatric symptoms, including depression and suicidal ideation, in association with the use of barbiturates (Campo et al. 1999); disruptive behavior and hyperactivity with barbiturates, vigabatrin, and possibly gabapentin; psychosis with ethosuximide; and encephalopathy in association with the use of valproate and phenytoin (Schmitz 1999). Antiepileptic drugs generally potentiate the actions of the inhibitory neurotransmitter GABA or attenuate the excitatory neurotransmission mediated by glutamate (Ketter et al. 1999).

While available research is lacking, the best available guidance suggests that the highest risk of seizures during therapeutic use is associated with the antidepressants bupropion, clomipramine, and maprotiline, the mood stabilizer lithium, and the antipsychotics clozapine and chlorpromazine; low-risk antidepressants include the SSRIs, MAOIs, mirtazipine, nefazodone, and trazodone, with the lowest-risk antipsychotics including haloperidol, molindone, pimozide, and risperidone (Alldredge 1999). While psychostimulants have been associated with the lowering of seizure threshold at high doses, stimulants such as methylphenidate have been considered to be relatively safe and effective in epileptic children with attention-deficit hyperactivity disorder (ADHD) (Crumrine et al. 1986; Feldman et al. 1989), and epileptic children who are seizure-free are unlikely to experience new seizures when methylphenidate is added to the regimen (Gross-Tsur 1997). Similarly, while adrenergic agents such as clonidine have been associated with seizures in overdose and can affect seizure threshold, they are considered to be relatively benign in relation to seizure control at therapeutic doses (Thiele 1999).

The ideal psychoactive agent in the patient with epilepsy should not antagonize GABAergic mechanisms or interfere with anticonvulsant blood levels (Curran and de Pauw 1998). Because drug-induced seizures are generally a dose-related phenomenon, using the lowest effective dose of psychoactive medication is recommended. Furthermore, it is generally wise to ensure that the antiepileptic regimen is optimal when psychopharmacological intervention is initiated. The clinician must remain alert to the possibility of drug-drug interactions with the antiepileptics, including the potential for increased risk of hepatotoxicity (Thiele et al. 1999). For example, a recent report cites the development of dyskinesia and bruxism with methylphenidate treatment in children being treated with val-

proate (Gara and Roberts 2000). While the potential for psychotropic agents to induce seizures in vulnerable individuals is certainly real, review of the available evidence and clinical experience suggest that psychopharmacological intervention can prove safe and rewarding in patients with epilepsy.

Psychopharmacological agents may be helpful in improving seizure control in some patients with epilepsy, perhaps by attenuating emotional arousal that may trigger seizures in vulnerable individuals, pharmacokinetic interactions with anticonvulsant medications (Allredge 1999), or by direct anticonvulsant effects, as have been reported with particular antidepressants (Dailey and Naritoku 1996), including fluoxetine (Favale et al. 1995).

Animal experiments have generated concerns that the use of antipsychotic medications might hinder neuronal recovery after traumatic brain injury, while stimulant treatment might facilitate recovery (Feeney et al. 1982). There is certainly reason to be cautious before initiating antipsychotic medication in an agitated child in the wake of a traumatic brain injury, but in the absence of more definitive evidence there is also no substitute for sound clinical judgment and a willingness to balance the potential risks and benefits of treatment with antipsychotics versus alternatives in such circumstances. Methylphenidate treatment has been reported to be beneficial in controlling symptoms of acquired ADHD in children who have experienced a traumatic brain injury (Mahalick et al. 1998), but available studies have been small and equivocal (Williams et al. 1998). SSRIs may be helpful in managing emotional symptoms associated with brain injury such as pathological crying (Andersen et al. 1999).

Diabetes Mellitus. The high rates of depression reported in diabetes mellitus (Kovacs et al. 1997) and the potential for depression to affect adherence to regimen and the tendency to develop adverse consequences such as retinopathy (Kovacs et al. 1995) suggest the possibility that active psychopharmacological treatment could be advantageous. The use of SSRIs has been associated with improved glycemic control in depressed diabetic adults (Carney 1998). There is also some evidence that SSRIs may reduce glucose levels in diabetics independent of insulin level and may be associated with some risk of hypoglycemia initially, but on balance SSRIs appear to be the agents of first choice in the treatment of depression in diabetes mellitus (Goudnick 1995). TCAs have been associated with decreases in glucose tolerance and increases in carbohydrate craving (Erenmemisogler et al. 1999), and the use of MAOIs is limited by the severity of induced hypoglycemia in some patients, weight gain, and the required diets (Goodnick et al. 1995). A study of poorly controlled diabetic adults found that an 8-week course of alprazolam treatment had a beneficial effect on metabolic control and levels of glycosylated hemoglobin regardless of anxiety level (Lustman et al. 1995).

Novel antipsychotic agents such as clozapine and olanzapine have been

associated with hyperglycemia and deterioration of glycemic control in diabetic patients, as well as weight gain and increased appetite, suggesting that clinicians should only use these agents with great caution and careful monitoring in diabetes mellitus (Wirshing 1998). Individuals treated with clozapine experience significant weight gain and lipid abnormalities and appear to be at greater risk for the development of diabetes (Henderson et al. 2000). Case reports have also implicated olanzapine in the development of hyperglycemia (Ober et al. 1999) and the development of diabetic ketoacidosis (Lindenmayer and Patel 1999). Individuals with diabetes also appear to be at increased risk for tardive dyskinesia when treated with traditional neuroleptics (Ganzini et al. 1991). Clonidine can stimulate the release of growth hormone and may be associated with hyperglycemia in diabetic patients (Mimouni-Bloch and Mimouni 1993).

Hematological Disorders. Blood dyscrasias such as agranulocytosis, aplastic anemia, and thrombocytopenia can occur in association with the use of a variety of psychoactive drugs. Agranulocytosis and aplastic anemia are the most serious and potentially deadly effects and have been reported in association with the use of the antipsychotic clozapine; the aliphatic phenothiazines thioridazine and chlorpromazine have also been associated with adverse hematological effects, although much less commonly (King and Wagner 1998). Fever, sore throat, and mucosal ulcerations may signal the development of neutropenia. There is little evidence for an increased risk of serious hematological reactions with high-potency neuroleptics such as haloperidol or with newer atypical agents, although neutropenia has rarely been reported with olanzapine (Cadario 2000), suggesting that ongoing vigilance is likely to be important. Other agents that have been implicated as having serious adverse hematological effects include the anti-convulsants carbamazepine and valproate, as well as mianserin and TCAs (Ayd 2000). Agranulocytosis was reported in a handful of patients in early clinical trials of mirtazapine, suggesting some reason to be cautious, but postmarketing experience has not revealed an unusual number of cases of hematological complications in association with the drug, and it is unclear if the original observation will prove significant (Preskorn 1999).

In addition to abnormalities of blood count, drugs may influence the function of particular blood cells. Most notable has been the association of abnormal platelet function and increased bleeding time with the use of SSRIs (Lake et al. 2000). SSRIs substantially decrease the intracellular concentration of serotonin in platelets and inhibit platelet function (Hergovich et al. 2000). Valproate has also been associated with disturbances of coagulation and reduced platelet activation (Zeller et al. 1999). Considerations about a psychoactive drug's potential to produce problems with bleeding can be quite important when making a medication choice in patients with a bleeding diathesis or who may be at special risk to be harmed by such effects.

Drug-Drug Interactions

Adverse drug events have been associated with prolonged length of stay, increased costs, and an increased risk of death, with pharmacokinetic drug interactions appearing to be a largely preventable and underappreciated problem (Classen et al. 1997). Drug-drug interactions occur when one drug alters the pharmacological effects of another concurrently administered drug, and are of potentially greater consequence when at least one of the drugs involved has a narrow therapeutic index (Nies and Spielberg 1996). Drug interactions may be pharmacodynamic or pharmacokinetic in nature, and both types of interactions may be operative in the same patient. It is critical that all current medications are known, and a special effort should be made to investigate whether the patient may be using nonprescription supplements or herbal remedies. The potential for drug-drug interactions should be anticipated prior to initiating psychopharmacological treatment, and the consultant should not hesitate to consult print resources, conduct a literature search, and/or request a consultation from the hospital pharmacy regarding potential pharmacodynamic or pharmacokinetic drug interactions. Though imperfect and often incomplete, the list of potential resources is growing (Strain et al. 1998). The majority of potential drug interactions are not absolute contraindications, but the potential for such interactions generally requires close monitoring and/or adjustments in dosage or administration schedule.

The greater the number of sites of action for a drug, the greater the potential for pharmacodynamic interactions with other drugs, with the types of interactions being determined by the specific sites of action (Preskorn 1999). An important example of a specific pharmacodynamic drug-drug interaction is the serotonin syndrome that occurs in association with the use of substances that increase the availability of serotonin within the central nervous system. It is a toxic state potentially manifested by neuromuscular symptoms such as restlessness, tremor, rigidity, head-shaking, hyperactive reflexes, myoclonus, confusion, seizures, and incoordination, as well as fever, sweating, diarrhea, hypertension, cardiac arrhythmias, cardiovascular collapse, and death (Sternbach 1991). Drug combinations that have been implicated include SSRIs or MAOIs in combination with one another or with tryptophan, dextromethorphan, meperidine, or TCAs such as clomipramine. Other than withdrawal of the offending agent or agents and supportive measures such as hydration and management of cardiovascular complications, little is known about treatment. Benzodiazepines such as clonazepam may be helpful for myoclonic symptoms, and agents with the ability to block serotonin receptors such as cyproheptadine may prove to be helpful.

Pharmacokinetic drug-drug interactions can affect any aspect of drug handling, including the absorption, distribution, biotransformation, and excretion of drugs. For example, aluminum- and magnesium-containing antacids can interfere with the absorption of neuroleptics, yet may increase the bioavailability of valproate (Lake et al. 2000). Nevertheless, pharmacokinetic drug interactions medi-

ated by the cytochrome P450 (CYP) enzyme system are the most common drug interactions of relevance in pediatric psychopharmacology. The CYP enzyme system is composed of at least 30 different heme-containing protein isoenzymes and is responsible for the oxidative metabolism of many endogenous and exogenous highly lipid-soluble compounds (Goldberg 1996). CYP enzymes are located primarily in liver, but are also found in gut, brain, and lung tissue. Oxidative metabolism is often the rate-limiting step in drug metabolism (e.g., phase I) and generally precedes conjugation of the substance in question via transferase enzymes (e.g., phase II). Activity of the CYP enzymes is believed to be most efficient in prepubertal children, declining to adult levels some time after puberty (Flockhart and Oesterheld 2000). CYP enzymes have been organized into families, designated by numerals, and subfamilies, designated by upper case letters, with individual isoenzymes in a subfamily being designated with a numeral as well (e.g., CYP 3A4). Isoenzymes within a family share commonalities in amino acid sequence of at least 40%, while those in subfamilies share 55% or greater (Lane 1996). Drugs may be identified as *substrates*, *inhibitors*, and/or *inducers* of CYP isoenzymes. A drug that is a substrate for a given CYP isoenzyme may or may not inhibit the metabolism of other drugs at the site; conversely, a drug that is an inhibitor of a particular CYP isoenzyme may or may not be metabolized at the site (Lane 1996). Similarly, a drug may induce CYP enzyme activity, potentially resulting in increased metabolism at the induced site. For example, the enzyme-inducing anticonvulsants carbamazepine and phenobarbital may lower the levels of clozapine and haloperidol when used in conjunction with these drugs (Thiele et al. 1999). Pharmacokinetic drug interactions are especially relevant when one of the involved drugs has a narrow therapeutic index. An example is provided by the development of delirium and renal failure due to tacrolimus toxicity in an organ transplant patient who was prescribed nefazodone, a potent inhibitor of CYP 3A4, the isoenzyme responsible for the biotransformation of the selective immunosuppressant agents tacrolimus and cyclosporine (Campo et al. 1998). Other important examples include prolonged QT intervals and the risk of sudden death when drugs such as astemizole, terfenadine, cisapride, pimozone, or thioridazine have been used in combination with drugs known to inhibit CYP3A.

The CYP enzymes most relevant to pediatric psychopharmacology are CYP 1A2, CYP2C9/10, CYP2C19, CYP2D6, and CYP3A (Flockhart and Oesterheld 2000). Table 1 contains a listing of some relevant substrates, inducers, and inhibitors for specific CYP enzymes. The reader is cautioned to avoid relying on such lists as the sole source of guidance regarding CYP-mediated drug interactions, as the listing is by no means comprehensive or definitive.

Mode of Administration

Mode of administration is an important consideration in medical settings, especially inpatient settings. Individual patients may be unable to take tablets or capsules and thus require the use of liquid oral preparations, or they may be unable

TABLE 1 Some Potential Substrates, Inducers, and Inhibitors for CYP Enzymes

CYP1A2*Psychotropic substrates*

Amitriptyline
Clomipramine
Clozapine
Fluvoxamine
Haloperidol
Imipramine
Olanzapine
Pimozide
Thioridazine

Other substrates

Acetaminophen
Caffeine
Ondansetron
Methadone
Propranolol
Tacrine
Theophylline

Inducers

Carbamazepine
Charbroiled meat
Cigarette smoke
Cruciferous vegetables
Omeprazole

Psychotropic inhibitors

Fluvoxamine (potent)

CYP2C9*Psychotropic substrates*

Amitriptyline
Fluoxetine
Sertraline
Valproate

Other substrates

Angiotensin II blockers (e.g., irbesartan, losartan, valsartan)
Nonsteroidal anti-inflammatories (e.g., diclofenac, ibuprofen, indomethacin, naproxen)
COX-2 inhibitors (e.g., celecoxib, meloxicam, rofecoxib)
Oral hypoglycemics (e.g., glipizide, tolbutamide)
Phenytoin
Tolbutamide
Torsemide
Warfarin

TABLE 1 Continued

<i>Inducers</i>
Carbamazepine
Phenobarbital
Rifampin
<i>Psychotropic inhibitors</i>
Fluoxetine (potent)
Fluvoxamine
Modafinil
Sertraline
Valproate
CYP2C19
<i>Psychotropic substrates</i>
Amitriptyline
Citalopram
Clomipramine
Diazepam
Imipramine
Moclobemide
Sertraline
Venlafaxine
<i>Other substrates</i>
Phenytoin
Proton pump inhibitors (lansoprazole, omeprazole, pantoprazole)
Cyclophosphamide
Indomethacin
Progesterone
Proguanil
<i>Inducers</i>
Carbamazepine
Rifampin
<i>Psychotropic inhibitors</i>
Citalopram
Fluoxetine (moderate)
Fluvoxamine (potent)
Modafinil
Topiramate
CYP2D6
<i>Psychotropic substrates</i>
Amitriptyline
Chlorpromazine
Citalopram
Clomipramine
Clozapine
Desipramine

TABLE 1 Continued

Fluoxetine
Fluvoxamine
Haloperidol
Imipramine
Maprotiline
M-CPP
Mirtazipine
Nortriptyline
Olanzapine
Paroxetine
Perphenazine
Risperidone
Sertraline
Stimulants (e.g., methamphetamine, methylphenidate)
Thioridazine
Trimipramine
Venlafaxine
<i>Other substrates</i>
Antiarrhythmics (e.g., encainamide, flecainide, mexiletine)
Antihistamines (e.g., mequitazine, promethazine)
Beta-blockers (e.g., metoprolol, propranolol)
Codeine
Dextromethorphan
Dihydrocodeine
Tramadol
<i>Inducers</i>
Pregnancy
<i>Psychotropic inhibitors</i>
Amitriptyline
Chlorpromazine
Citalopram (mild)
Clomipramine
Desipramine
Diphenhydramine
Fluoxetine (potent)
Haloperidol
Imipramine
Moclobemide
Nortriptyline
Paroxetine (potent)
Perphenazine
Pimozide
Reboxetine

TABLE 1 Continued

Sertraline (mild)
Thioridazine
Venlafaxine (mild)
CYP 3A
<i>Psychotropic substrates</i>
Alprazolam
Amitriptyline
Buspirone
Carbamazepine
Citalopram
Clomipramine
Clonazepam
Clozapine
Diazepam
Fluoxetine
Haloperidol
Imipramine
Midazolam
Mirtazipine
Nefazodone
Quetiapine
Pimozide
Reboxetine
Risperidone
Sertraline
Trazodone
Triazolam
Zalepon
Zolpidem
<i>Other substrates</i>
Acetaminophen
Amiodarone
Astemizole
Calcium channel blockers (e.g., diltiazem, felodipine, nifedipine, verapamil)
Cisapride
Cyclosporine
Codeine
Ethosuximide
Felbamate
Fentanyl
Lamotrigine
Lidocaine
Loratidine
Lovastatin

TABLE 1 Continued

Macrolide antibiotics (e.g., clarithromycin, erythromycin)
Methadone
Quinidine
Ritonavir
Steroids (e.g., cortisol, estradiol, hydrocortisone, progesterone, testosterone)
Tacrolimus
Terfenadine
Vinblastine
<i>Inducers</i>
Alcohol
Carbamazepine
Corticosteroids
Felbamate
Phenobarbital
Rifampin
Venlafaxine
<i>Psychotropic inhibitors</i>
Fluoxetine (mild)
Fluvoxamine (moderate)
Nefazodone (potent)

Source: Alpert et al. 1997; Preskorn 1999; Flockhart and Oesterheld 2000.

to take any medications orally and thus require parenteral administration. Developing a sense of familiarity with types of preparations available for a given agent or class of agents can be beneficial in such circumstances.

COMMON CLINICAL PROBLEMS

Delirium

Delirium represents a true pediatric psychiatric emergency, yet there is little research specific to children and adolescents that is available to guide clinical practice. The condition has also been described with terms such as “encephalopathy” or “acute confusional state” in pediatric medical settings and is defined by a disturbance or impairment in arousal or consciousness that most often develops acutely, and which may be associated with reduced ability to shift or focus attention, fluctuation in level of consciousness, disorientation, memory impairment, disorganized thinking, changes in activity level, sleep-wake cycle disturbances, emotional disturbances, and perceptual problems such as hallucinations (APA 1994). Delirium is common in physically ill and hospitalized children and may

herald a rapidly deteriorating and potentially fatal medical condition (Prugh et al. 1980), but it may be underdiagnosed and undertreated in pediatric settings. Delirium in childhood may be misconstrued as developmental regression in the face of stress or simply a manifestation of disruptive or “naughty” behavior, particularly when associated with agitation and overactivity (Prugh et al. 1980). Conversely, delirium should be included in the differential diagnosis whenever the clinician is confronted with an agitated child or adolescent.

Established risk factors for delirium include preexisting brain damage, polypharmacy, substance intoxication or withdrawal, multiple medical problems, organ failure, burns, and hypoalbuminemia (Trzepacz 1996). More of the unbound portion of drugs that are protein bound may become biologically available in hypoalbuminemia with a consequent increased risk of drug activity and side effects. Medications with anticholinergic activity are often implicated in delirium, and it should be remembered that many commonly prescribed drugs (e.g., digoxin, cimetidine, ranitidine, theophylline) not generally considered to be anticholinergic do have finite anticholinergic effects, making the prescription of multiple medications or polypharmacy particularly problematic in the medically ill (Tune et al. 1992). While the elderly do appear to be at greater risk for delirium, clinical teaching has propagated the belief that the very young are also more susceptible, based primarily on the observation that children can become delirious with high fevers, but there is actually little credible supportive evidence, and children appear less likely to become delirious following cardiomy than adults (Ryan 1998).

Delirium can be an important clue to undiagnosed or underappreciated physical disease. The medical differential diagnosis of delirium is exhaustive and beyond the scope of this chapter but includes virtually any serious or life-threatening medical condition sufficiently advanced to impact cognitive function (Campo 1993; Ryan 1998). In subtle cases where clinical uncertainty exists as to whether a given child may be suffering from delirium, the electroencephalogram (EEG) may prove a useful tool, with slowing of background rhythms being the most common but not exclusive finding, meaning that a diffusely slow tracing can confirm the diagnosis of delirium, but a normal or fast record does not rule out the diagnosis (Prugh et al. 1980; Ryan 1998). Given variabilities in the EEG background activity, comparison of the EEG with a prior EEG can be helpful if a previous tracing is available (Campo 1993). Given the potential seriousness and predictive value of delirium, careful medical work-up is indicated, as the definitive management of delirium requires identification of and correction of the underlying physical disturbance.

Management thus ideally begins with efforts to reverse or ameliorate the physical cause or causes of the delirium. Environmental manipulations are especially important, with the most important single intervention being the presence of a parent, family member, or other familiar adult. The safety of the patient and

others must be ensured, with the delirious patient generally requiring constant supervision and protection. Ongoing support, reassurance, and reorientation by family and staff are helpful, as are the use of calendars and other efforts to create a more familiar and less threatening environment through the use of nightlights, limiting noise and overstimulation, and controlling pain (Trzepacz 1996; Ryan 1998).

Active symptomatic treatment of the core symptoms of delirium is largely pharmacological pending resolution of the causative physical disturbance, with the high-potency antipsychotic medications currently being considered the treatments of choice (APA 1999). Haloperidol is the agent most commonly used given few anticholinergic side effects, few active metabolites, a relatively low risk of sedation or cardiovascular side effects such as hypotension, a long history of experience with the drug in the physically ill, and the availability of oral, intramuscular, and intravenous administration. Haloperidol is the best studied somatic intervention for delirium, but systematic pediatric trials are lacking, and intravenous administration, though widely used and preferred by most clinicians in the acute care setting, has not been approved by the FDA. Some evidence suggests that extrapyramidal side effects are less likely when the drug is used intravenously (Manza et al. 1987). The most serious risk associated with the use of haloperidol in the delirious patient is related to lengthening of the QT interval and the risk of polymorphic ventricular tachycardia or torsades de pointes, which has been reported with both high and low doses and both intravenous and oral administration (Jackson et al. 1997; Sharma et al. 1998). A baseline electrocardiogram should be obtained, with attention paid to the length of the QT interval, and the tracing monitored during the treatment of delirium with antipsychotic medication; attention should also be paid to serum levels of magnesium and potassium (APA 1999).

There are no pediatric studies to guide dosing of haloperidol in delirium. It is generally advisable to individualize treatment, beginning with low doses and titrating the dose accordingly. In the absence of marked agitation, total daily doses of 1–2 mg divided twice daily for oral administration or every 4–6 hours when given intravenously may be sufficient and well tolerated. Titration to higher doses may be necessary over time depending on neurocognitive symptom control or in the presence of agitation, with a rough rule of thumb in children being 0.5 mg for mild agitation, 2 mg for moderate agitation, and 5 mg for more severe agitation (Ryan 1998). While caution with dosing is certainly warranted, the distress and potential for real harm coming to the agitated child argues for prompt and decisive intervention, which is generally justifiable given the relative safety of haloperidol in the controlled medical setting. It is advisable to continue patients on a standing dose of medication rather than to rely on intermittent doses of medication to treat outbursts of agitation, with aggressive but methodical tapering

of the medication once symptomatic control has been achieved and the delirium appears to have cleared.

The related butyrophenone droperidol has also been employed in the management of delirium and acute agitation and is generally considered to have a more rapid onset of action and to be slightly more likely to produce sedation and hypotension than haloperidol. Droperidol has also been associated with lengthening of the QT interval, torsades de pointes, and sudden death and is not available for oral administration (APA 1999). Low-potency phenothiazines such as chlorpromazine and thioridazine have also been employed in delirium, though generally less commonly due to more prominent anticholinergic effects, sedation, and α -adrenergic-blocking activity that can result in hypotension. The newer atypical agents risperidone, olanzapine, and quetiapine are increasingly being used in the management of delirium, though the available literature has been limited to case reports (APA 1999). Monotherapy with benzodiazepines may not be effective except in the specific circumstances of alcohol or benzodiazepine withdrawal, and their use has been associated with disinhibition and paradoxical reactions in adolescents (Coffey 1990). However, there have been reports of the utility of benzodiazepines in delirium when used in combination with antipsychotic medications, with some studies of the intravenous use of lorazepam and haloperidol suggesting improved efficacy with the combination and fewer extrapyramidal side effects (Menza et al. 1988). Such a combination might be worthy of consideration in circumstances where agitation is prominent and not controlled by moderate or higher doses of antipsychotic medication.

Transplantation

In addition to dealing with issues related to organ failure per se, adverse drug interactions are an especially relevant concern in organ transplantation, given the multiple medications often prescribed, the pharmacokinetic and pharmacodynamic complexities associated with organ failure, and the narrow therapeutic index of immunosuppressant agents such as cyclosporine and tacrolimus (Trzepacz et al. 1993a,b). This is particularly problematic in organ transplantation, where changes in levels of immunosuppressant medication may result in not only serious toxicity, but also changes in the degree of immunosuppression, with low immunosuppressant levels putting the patient at greater risk of rejection. Both tacrolimus and cyclosporine, the most commonly used immunosuppressants, are metabolized primarily by CYP3A (Seifeldin 1995). The pharmacological management of depression in patients who have undergone organ transplantation is thus especially challenging and requires attention to the physiological and pharmacological aspects of each new case. The use of a potent inhibitor of CYP3A like nefazodone in combination with the selective immunosuppressants can be

particularly problematic and result in life-threatening toxicity, making other antidepressants with minimal CYP inhibition like citalopram or agents such as paroxetine, a CYP2D6 inhibitor, better choices if all other things are considered equal (Campo et al. 1998).

Despite widespread use in pediatric transplantation, tacrolimus and cyclosporine have not been compared systematically regarding the potential for adverse neuropsychiatric or cognitive effects in children. Painfully little is known regarding the cognitive, emotional, and behavioral consequences of transplantation, but a number of studies suggest that pediatric organ transplantation may be associated with adverse psychological consequences (Stewart et al. 1994; Wray et al. 1994; Serrano-Ikkos et al. 1999). A recent study found that while children who underwent cardiac or cardiopulmonary transplantation did not differ preoperatively on measures of psychiatric symptoms and disorder from those undergoing conventional cardiac surgery, the prevalence of psychiatric difficulties was significantly greater in the transplantation group one year postoperatively (Serrano-Ikkos et al. 1999). Another study found that recipients of pediatric heart and heart-lung transplants performed significantly worse on measures of cognitive function posttransplant than children undergoing conventional surgery and those in a well comparison group (Wray et al. 1994). Though additional studies are clearly needed, there is considerable evidence that both cyclosporine (Grimm et al. 1996; Gijtenbeek et al. 1999) and tacrolimus (Torocsik et al. 1999) have been associated with frank neurotoxicity, as well as adverse neuropsychiatric effects such as apparent anxiety and akathisia (DiMartini et al. 1991; DiMartini et al. 1996; Sing et al. 2000).

HIV/AIDS

Treatment with antiretroviral medications has improved survival and slowed disease progression in HIV-infected children and adolescents, but psychiatric disorders are relatively common in this population (Havens et al. 1994). HIV infection in childhood has been associated with loss of acquired neurocognitive skills and developmental delays, but antiretroviral drug treatment can be successful in reducing morbidity and even with reports of improvements in mental abilities (Raskino et al. 1999; Wolters et al. 1994). Changes in mental status or the development of new psychiatric symptoms in the HIV-infected patient require that other potentially treatable and reversible causes of the symptoms are ruled out, particularly infections, when counts are low or the viral load has begun to rise. HIV is associated with a variety of psychiatric diagnoses and symptoms, including dementia, delirium, depression, and mania, and symptoms such as fatigue, wasting, and asthenia are common (APA 2000). Before moving to symptomatic treatment of psychiatric symptoms associated with HIV, it should be remembered that targeting the underlying HIV infection with antiretroviral therapy can serve

as the foundation of intervention, particularly with HIV-associated dementia and mania secondary to the effects of HIV infection (Ellen et al. 1999). Equally important is to consider whether there may be psychiatric effects related to antiretrovirals, as manic syndromes have been reported in association with their use (Maxwell et al. 1988).

Principles of psychopharmacological intervention are similar to those in other medically ill patients. However, individuals with advanced HIV infection and on complex antiretroviral regimens may be more sensitive to medication side effects and at especially high risk for drug-drug interactions (Ayuso 1994). The use of antipsychotic medications has been reported to be associated with an increased risk for extrapyramidal side effects in the HIV-infected population, and atypical agents are likely to be better tolerated (Singh et al. 1997). SSRIs appear to be better tolerated as antidepressants in HIV-infected individuals than TCAs (Schwartz and McDaniel 1999). Care must also be exercised in attending to the potential for drug interactions, particularly with potent inhibitors of CYP3A such as nefazodone or agents that may have serious cardiovascular side effects if levels climb, such as pimozone. It is generally recommended to use low initial doses of psychoactive medications in this population and to titrate the dose upward slowly, being vigilant for potential drug interactions. Agents with less likelihood to inhibit the CYP system such as citalopram and mirtazapine may be particularly appealing, with the latter agent being potentially helpful for patients with sleep difficulties or poor appetite.

Choice of an antidepressant, mood stabilizer, or antipsychotic may be influenced by the antiretroviral regimen, given the frequency of drug interactions and the potential for P450-based interactions. For example, the protease inhibitor ritonavir is an inhibitor of CYP3A, CYP2D6, and CYP2C9/19, while the other protease inhibitors such as indinavir, nelfinavir, and saquinavir primarily inhibit CYP3A. Conversely, the reverse transcriptase inhibitors nevirapine and efavirenz are metabolized by CYP3A and CYP2B6 and can potentially result in decreased psychotropic drug concentrations (APA 2000). Gabapentin has been used to treat the peripheral neuropathy that can be associated with HIV infection and/or the use of some antiretrovirals and is less likely than other anticonvulsants to result in drug-drug interactions.

Cachexia, Wasting, and Fatigue

Progressive weight loss associated with the erosion of fat and muscle mass is common in patients with advanced cancer or AIDS and is frequently associated with symptoms of anorexia, nausea, and asthenia. Drugs such as corticosteroids and anabolic steroids like oxandrolone, testosterone, and somatotropin, progestational agents such as megestrol, cannabinoids such as dronabinol, and thalidomide have been reported to be helpful in the treatment of such symptoms in

patients with cancer or HIV/AIDS (Bruera and Neumann 1998; APA 2000). Stimulants have also been used in the management of fatigue and depression in seriously ill adults (Olin and Masand 1996), including those with HIV (Wagner et al. 1997), and have also been reported to be useful in the management of opiate-associated sedation in adolescents (Yee and Berde 1994).

Pain

Pain is an unpleasant sensory and emotional experience that is associated with tissue damage or perceived as representative of such damage (Basbaum and Jessell 2000). Pain and nociception are not equivalent, as all perception involves an abstraction and elaboration of sensory inputs. Pain is subjective, and must always be assessed through self-report. No definitive objective measurement technique exists, making pain particularly difficult to assess and manage in infants and young children due to their limited self-reporting abilities. Tissue damage can sensitize nociceptors and thus enhance the painful sensation associated with a given stimulus. Hyperalgesia may develop at the site of tissue damage, perhaps consequent to changes in nociceptor sensitivity, but may also develop in surrounding, presumably undamaged areas, possibly due to sensitization of collateral nociceptor branches or of centrally located neurons as a result of sustained activity. Pain can also arise spontaneously in the absence of nociceptor activity or can be minimal or absent in the presence of great nociceptor activation, suggesting central modulation of peripheral nociception. Pain is a common experience across a variety of physical disorders. Neuropathic pain is associated with direct injury to nerves in the peripheral or central nervous system, and often has a burning or "electric" quality. Examples of neuropathic pains include postherpetic neuralgia, reflex sympathetic dystrophy, diabetic neuropathy, and phantom limb pain, as well as much of the pain associated with cancer or AIDS (Breitbart 1998).

Though most of the commonly used psychoactive medications are not substitutes for primary analgesics such as acetaminophen, nonsteroidal anti-inflammatory agents, and opiates, many psychopharmacological agents have been employed as adjuvant medications for pain, including antidepressants, anti-convulsants, antipsychotics, and stimulants (Lynn 1990). Adjuvant medications may be especially useful when traditional analgesics such as narcotics are ineffective or side effects problematic. There is considerable evidence that TCAs are analgesic and useful in the management of both neuropathic and nonneuropathic pain in adults and some evidence that novel antidepressants such as SSRIs and trazodone have related properties (Breitbart 1998). Psychostimulants such as dextroamphetamine and methylphenidate have been used to counteract the sedation that can sometimes interfere with the effective use of opiates in children with

cancer or other types of intractable pain (Yee and Berde 1994) and may potentiate the analgesic effects of opiates (Bruera and Neumann 1998).

A problem commonly faced in dealings with seriously ill children and adolescents is the management of opiate and benzodiazepine dependence, with these agents being the most widely used drugs to manage pain and effect sedation in pediatric settings. Use of such drugs for more than 5–10 days has been associated with the development of tolerance and dependence, with continuous infusions of potent drugs such as fentanyl and high duration of receptor occupancy being considered factors in increasing risk for both (Yaster et al. 1996). The potential for withdrawal syndromes in such patients argues for the practice of tapering such medications in hospital settings, with a general approach first involving efforts to convert the patient from continuous infusion to bolus therapy, then from parenteral to oral medication. While it is generally acceptable to use the same opiate or sedative over the process of weaning, it may sometimes be desirable to switch to a different preparation based on considerations related to ease of administration, duration of action, and convenience with tapering, as agents with longer half-lives may be somewhat easier to taper. It is thus essential that dose equivalence is maintained if a switch in type of medication is made. The approach recommended by Yaster et al. (1996) involves beginning to taper only after an intermittent regimen has been achieved and then decreasing the dose by 10–20% per day. Once the lowest doses of convenience are obtained, usually after a week or so, the interval of dosing is increased and then therapy is stopped completely. The authors then employ clonidine to treat symptoms of withdrawal, although the risk of seizure with benzodiazepine withdrawal argues for the judicious use of long- to intermediate-acting benzodiazepines.

Migraine

Migraine is a disorder of special interest to psychiatrists given the powerful associations demonstrated between migraine, anxiety, and depression (Merikangas and Stevens 1997). A variety of psychopharmacological agents have been noted to be of potential benefit in the prevention of migraine headaches, with antidepressants, anticonvulsants, and beta-adrenergic blockers playing prominent roles (Solomon 1995). Serotonergic transmission is considered to play a prominent role in migraine, and pediatric experience suggests that pizotifen (Symon and Russell 1995) and cyproheptadine (Worawattanakul et al. 1999) may be of benefit in the prophylaxis of abdominal migraine. Propranolol has also been reported to be of benefit in abdominal migraine (Worawattanakul et al. 1999). A double-blind placebo-controlled crossover study of 40 children and adolescents with migraine suggests that trazodone may be useful as a prophylactic agent in pediatric migraine (Battistella et al. 1993). The pediatric literature is relatively lacking in

comparison to the adult literature, where studies have demonstrated that TCAs, SSRIs, and other novel antidepressants (O'Malley et al. 1999), including the S-enantiomer of fluoxetine (Steiner et al. 1998), are helpful as prophylactic agents for migraine. The situation is similar with the anticonvulsants, with several double-blind studies confirming the efficacy of valproate as a prophylactic agent in adults (Silberstein 1996).

Because the newer treatments for the acute treatment of migraine such as sumatriptan affect serotonergic neurotransmission, there has been some concern about the possibility of inducing a serotonin syndrome when such drugs are used in conjunction with serotonergic antidepressants, a particularly relevant issue given the frequent use of antidepressants in individuals with migraine. Available experience with the combined use of sumatriptan and antidepressants such as SSRIs has been reassuring and suggests that the combination is relatively safe (Blier and Bergeron 1995; Putnam et al. 1999). Despite the popularity of newer serotonergic acute treatments for migraine like sumatriptan, antipsychotic medications such as chlorpromazine and prochlorperazine have been demonstrated to be efficacious in the acute management of migraine at levels comparable to sumatriptan or metoclopramide (Coppola et al. 1995; Kelly et al. 1997). Butyrophenones such as haloperidol and droperidol may also be useful in the management of acute migraine (Richman et al. 1999). The relative safety of antipsychotic medications when used acutely makes them worthy of consideration when confronted with acute or intractable migraine providing that the potential for extrapyramidal and other side effects is kept in mind.

Somatization and Somatoform Disorders

There have been no systematic studies of psychoactive medications in pediatric somatization or situations where children present with physical symptoms that appear to be medically unexplained (Campo and Garber 1998). Pediatric somatization and frequent complaints of pain have been associated with an increased risk of concurrent psychopathology, functional impairment, and greater health service use (Campo et al. 1999), and functional abdominal pain in childhood appears to predict anxiety and emotional disorder in adulthood (Campo et al. 2001). Psychopharmacological interventions may prove useful in the treatment of medically unexplained recurrent pain, gastrointestinal distress, or fatigue in children and adolescents but have not been studied for this use in the pediatric population. Antidepressants and anxiolytics have been shown to reduce somatic symptoms in internalizing psychiatric disorders in adults (Simon et al. 1998). A recent meta-analysis of antidepressant treatment studies addressing so-called psychogenic pain and somatoform pain disorders in adults found that antidepressants appear to be of significantly greater benefit than placebo (Fishbain et al. 1998). Another meta-analysis examined the use of a variety of antidepressant

medications for medically unexplained physical symptoms and associated symptom complexes such as headache, fibromyalgia, and functional gastrointestinal disorders, and suggested that antidepressants may be helpful for specific physical symptoms as well as the described symptom complexes (O'Malley et al. 1999). A recent critical review of treatments for irritable bowel syndrome (IBS) suggested that antidepressant medications were associated with global improvements in affected patients, but the small numbers and suboptimal quality of available studies limited the conclusions that could be drawn (Jailwala et al. 2000). Though most prior studies have employed TCAs, case reports and case series suggest that SSRIs such as paroxetine (Kirsch and Louie 2000) and fluvoxamine (Emmanuel et al. 1997) may be of benefit as well. There is also preliminary evidence for the usefulness of SSRIs in treating adults with hypochondriacal beliefs and concerns (Kellner 1992) and with body dysmorphic disorder (Phillips 1996). Comparable work in children and adolescents is yet to be accomplished. In some patients who experience physical symptoms predominantly associated with emotional arousal and anxiety, a short course of a benzodiazepine can provide symptomatic relief and help reassure the patient and family that emotional distress is operative (Campo and Garber 1998). As with other interventions, a successful response to treatment can help reassure the patient and family that the original somatoform diagnosis was correct and serious physical disease unlikely, thus allowing psychiatric and rehabilitative treatments to proceed.

Pregnancy and Premenstrual Disorders

Though controlled studies of adolescent populations are not available, it is worth mentioning that although there is still much to be accomplished, considerable progress has been made in understanding and managing psychiatric disorders in association with the menstrual cycle and pregnancy in women. For example, both retrospective and prospective studies have been encouraging in their findings that the use of antidepressants in pregnancy, particularly SSRIs, does not appear to be associated with fetal death or major birth defects and that available evidence to date has not identified any developmental differences between children exposed to antidepressants in utero and those who have not been so exposed (Wisner et al. 1999). The use of antidepressants near term can nevertheless be associated with direct drug effects and even antidepressant withdrawal syndromes in neonates. Pregnancy can also have effects on renal and hepatic metabolic activity, requiring vigilance in dosing and the prevention of drug-drug interactions (Ayd 2000). Evidence is also accumulating that antidepressants are helpful in the treatment of the symptom constellations referred as premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). There is some evidence suggesting that a relative serotonin depletion is associated with PMDD, and SSRIs have been shown to be of benefit in both PMDD and PMS, with SRIs appearing

to be superior to TCAs and bupropion in PMDD (Eriksson et al. 1995; Pearlstein et al. 1997; Freeman et al. 1999). Other agents such as alprazolam may also be of benefit in premenstrual disorders (Freeman et al. 1995).

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Pharmacological Treatment of Substance Abuse Disorders

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The use and abuse of alcohol and other illicit substances by adolescents is a common phenomenon. In 1999, approximately half of high school seniors and over 20% of eighth graders reported having used marijuana at some point in their young lives (Johnston et al. 1999). Six percent of seniors reported daily cannabis use. Approximately 30% of seniors and 15% of eighth graders reported drinking five or more drinks in a row in the preceding 2 weeks. Despite being a common occurrence, substance use among adolescents is not always a benign behavior. Problems associated with substance use among adolescents include suicide, unintentional injuries, such as motor vehicle accidents and drownings, and increases in risk-taking behaviors (Bukstein 1995). Substance use and use disorders are a major cause of morbidity and mortality among adolescents (CDCP 2000).

As pharmacological treatments take an increasingly more important role in the intervention of adults with substance use disorders (SUDs) (Solhkhah and Wilens 1998; Kranzler et al. 1999), medications may also have a potential role for adolescents with SUDs. Clinicians who are confronted with evaluating and treating adolescents with substance use problems need to be familiar with a host

of issues related to the characteristics of adolescents who use and abuse substances, the types and characteristics of the substances that they use, the literature supporting the pharmacological treatment of these youths, and, finally, practical considerations in the pharmacological treatment of adolescents with SUDs. This chapter will review these issues, including (1) the conceptualization of adolescent SUDs, (2) the epidemiology of adolescent use and SUDs, (3) pharmacological concepts relevant to substance use disorders, and (4) treatment strategies.

CONCEPTUALIZATION OF THE DISORDER

The Development of Substance Use and Use Disorders

Although adolescents begin their substance use at a range of ages, there appears to be a consistent sequence of stages for the involvement with substances by children and adolescents. Kandel and associates (Kandel 1975; Yamaguchi and Kandel 1984) originally reported these stages and much of their work has been confirmed by other investigators (Brook et al. 1982; Huba and Bentler 1982; Donovan and Jessor 1983b). In this substance involvement sequence, adolescents first try “gateway” substances, such as beer, wine, and cigarettes, that are legal (to adults) and more readily available to youth. The use of alcoholic beverages generally precedes the use of marijuana and the subsequent use of other illicit drugs, although marijuana may be more commonly a gateway drug for specific populations such as African American youth (Kandel and Davies 1992; Kandel and Chen 2000). Almost all adolescents enter at the earliest stages and successively fewer progress to later, more serious levels of substance use. There is strong evidence for stage-specific antecedents, predictors, or risk factors. Many risk factors or characteristics associated with entry into one stage or the progression to another stage of adolescent substance use may not be as important in the transition to another stage (Kandel et al. 1978). For example, greater peer involvement and minor delinquent activities predict initiation into the earliest stages of use, while poor parental relations and deviant attitudes and behavior are more important in the progression to later stages. The literature on the development of substance use behaviors has given minimal attention to neuropsychiatric factors that might influence the development of substance use and substance use disorders in adolescents.

Diagnosis

The core concept of substance use disorder is a persistent pattern of use despite the occurrence of negative consequences. Prominent among the potential negative consequences of substance use disorders in youth are neuropsychiatric sequelae manifested as internalizing or externalizing symptoms. Although the neuropsychiatric consequences of substance use and abuse among adults is well docu-

mented (Fals-Stewart et al. 1994), the neurobehavioral correlates of substance use and abuse among adolescents are not well understood. The neuropsychiatric effects of substance use are important in that these effects are often features of substance use disorders. For a diagnosis of substance abuse based on criteria of the *Diagnostic and Statistical Manual*, Fourth Edition (APA 1994), the substance user displays a maladaptive pattern of substance use leading to clinically significant impairment or distress. Such a maladaptive pattern of use can be manifested by use resulting in failure to fulfill major role obligations and/or continued use despite social or interpersonal problems caused or exacerbated by substance use. The neuropsychiatric effects of substances may mediate these problems. For a diagnosis of substance dependence, a maladaptive pattern of substance use can be manifested by use despite knowledge of having a persistent or recurrent physical or psychological problem that is caused or exacerbated by substance use. Neuropsychiatric effects can be among these problems.

EPIDEMIOLOGY

Not all children and adolescents who use psychoactive substances, even on a regular basis, develop problems or ultimately substance use disorders (Bukstein and Kaminer 1993). Although surveys pertaining to substance abuse or dependence among the general population of adolescents are limited, existing reports suggest that a sizable number of adolescents develop problems at some point before adulthood. Reinharz and associates (1993), for example, found a lifetime prevalence of 32.4% for alcohol abuse/dependence and 9.8% for drug abuse/dependence among a community sample of older adolescents. Similarly, other surveys have reported that approximately 30% of adolescent males acknowledge a pattern of problem drinking (Donovan and Jessor 1978).

Studies such as Monitoring the Future (MTF), conducted by the University of Michigan's Institute for Social Research (Johnston et al. 1999), and the Youth Risk Behavior Surveillance System (YRBSS) carried out by the Centers for Disease Control and Prevention (CDCP 2000) have collected information on adolescent substance use for many years. For example, the MTF has collected information on adolescent drug use in the eighth, tenth, and twelfth grades, along with such questions as availability of substances and perception of risk of taking substances since 1975. The YRBSS has measured adolescent drug use in high school students with special attention to gender and ethnicity since 1990.

According to the results of the 1999 MTF study of high school students (NIDA, 2000), there was a decline in the annual prevalence rates for most drugs after reaching recent peak levels in the mid-1990s. In 1999, 54.7% of twelfth grade students reported ever having used any illicit drug and 80% alcohol. Eighth graders reported lifetime use rates of 28.3% for illicit drugs and over 50% alcohol. The rate for twelfth graders is less than the previous high set in 1981 of 65.6%,

but the lifetime prevalence within this group has increased from 40.7% in 1992 to 54.7% in 1999. Similar trends can be seen among younger groups of high school and junior high students. Specific drugs of abuse measured by the MTF include alcohol, cigarettes, marijuana, inhalants, LSD, cocaine, and heroin. Alcohol has the highest rate of use among adolescents, with over 80% trying it before leaving high school. While only 3.4% of seniors reported daily alcohol use, 30.8% reported drinking at least five drinks on a single occasion in the preceding 2-week period. For eighth graders, 9.4% report being intoxicated 30 days prior to the MTF survey. The second most commonly used drug is nicotine, with over 11 percent of twelfth graders using at least one half pack of cigarettes on a daily basis. Almost 50% of seniors and 22.0% of eighth graders reported having used marijuana use at least once. Daily marijuana use was reported by 6.0% of twelfth graders and 1.4% of eighth graders. Lifetime inhalant use was highest amongst eighth graders at 17.7%. Most steroid users are male, and in the previous year, use of steroids was reported by 2.2% of eighth graders, 3.6% of tenth graders, and 2.5% of twelfth graders.

Of recent interest are lifetime prevalence rates for two stimulants: methamphetamine (“ice”) and MDMA (methylenedioxymethamphetamine) or “ecstasy.” In 1999, 8.0% of seniors reported ever having used ecstasy and 4.8% “ice,” respectively; 2.5% of twelfth graders reported ecstasy use in the preceding month.

The use of drugs varies by gender and ethnicity. YRBSS data show males being more likely to engage in the following drug habits when compared to female peers: episodic heavy drinking, lifetime and current marijuana use, current cocaine use, and initiating cigarette, alcohol, and marijuana use before the age of 13 years (CDCP 2000). White students were more likely than Hispanic or black students to currently use alcohol, cigarettes, inhalants, and cocaine. However, Hispanic students reported a greater lifetime use of cocaine along with initiating marijuana use before the age of 13 when compared to white students.

The evidence of the coexistence or comorbidity of substance abuse disorders and other psychiatric disorders is well documented in adults. In the Epidemiologic Catchment Area Study, a large epidemiological study of adult mental health problems, 37% of adults reported having either disorder (Regier et al. 1990). There was a 2.7 times greater risk of having some substance use disorder with a lifetime prevalence of about 29% in patients with combined or coexisting psychiatric disorders.

The rate of co-occurrence or comorbidity between psychiatric disorders in adolescents is high (Offord and Fleming 1991). There are few community studies of the prevalence of SUD comorbidity in adolescents. The Oregon Adolescent Depression Project (OADP) (Lewinsohn et al. 1993) assessed lifetime comorbidity in 1710 high school students and reported that 66.2% of adolescents with SUD had an additional lifetime comorbid disorder compared to 31.3% of adolescents

without a SUD. Adolescents with SUD reported a lifetime prevalence of 25.4% for any disruptive behavior disorder, 49.4% for any mood disorder, and 16.2% for any anxiety disorder. In the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study of mental disorders in the community, adolescents aged 14–18 years old diagnosed with a current SUD were 1.5 times more likely to be diagnosed with any anxiety disorder, 3.7 times more likely to be diagnosed with any mood disorder, and 20.3 times more likely to be diagnosed with a disruptive behavior disorder than adolescents without current SUDs (Kandel et al. 1999). Comparisons with adult samples such as the ECA and the National Comorbidity Survey suggest that comorbidity rates for adolescents are the same as those for adults (Kessler et al. 1997). In the MECA study, 76% of adolescents with SUDs had at least one comorbid psychiatric disorder, while only 27.8% of adolescents without SUDs had a psychiatric disorder.

In studies of clinical populations, the rate of SUD comorbidity in adolescents is even higher, with depressive disorders ranging approximately 40–50%, conduct disorder 80% in some clinical populations, ADHD up to 30%, and anxiety disorders up to 40% (Greenbaum et al. 1991; Bukstein et al. 1992; Riggs et al. 1995; Clark et al. 1997; Weinberg et al. 1998).

Existing research of adolescent comorbidity in clinical populations suffers from significant methodological problems, including the lack of a valid, reliable nosology and specific criteria for substance use disorders in adolescents, problems in assessment methods, and variations in the populations assessed (Bukstein et al. 1989). Because the existing studies examine the occurrence of comorbidity of substance abuse and other psychiatric disorders, comorbidity may be a function of severity. Patients with comorbid disorders may be more severely impaired and thus are likely to seek and enter treatment. Such a selection or referral bias, also known as Berkson's bias (Berkson 1946), may lead to misleading associations between substance abuse and coexisting psychiatric disorders. However, we treat those who seek treatment or who are brought in by others (usually in the case of adolescents), therefore existing studies of clinical population are useful in describing the characteristics of our patients. In clinical samples of adolescents with SUDs, psychiatric comorbidity is the rule rather than the exception.

PHARMACOLOGICAL CONCEPTS RELEVANT TO SUBSTANCE USE DISORDERS

Although environmental factors such as early involvement with deviant peers, parental substance use and abuse, and deficiencies in parental monitoring and supervision of activities have a large role in the early stages of adolescent substance use, compulsive patterns of substance use are primarily motivated by the reinforcing consequences (Jaffe 1990; Gardner 1992). In effect, these substances are consumed either to induce a state of euphoria (positive reinforcement) or to

relieve the person from an aversive mood state (negative reinforcement). Some abusable drugs have no primary reinforcing effects (e.g., hallucinogens, anabolic steroids), but the consumption of these substances is regulated primarily by secondary (learned) reinforcers. All abusable substances have specific neuropsychiatric effects, that is, they change behavior, mood, and cognition. When used as a positive reinforcer, alcohol or other drugs may enhance one or more of these effects. When used as a negative reinforcer, alcohol or other drugs may ameliorate problems in mood, cognition, and behavior. In addition to their behavioral pharmacological effects, the acute and lasting effects of abusable drugs may also manifest as neuropsychiatric disturbances (i.e., symptoms or disorders).

Drug reinforcement involves activation of the dopaminergic system subserving reward centers of the brain (Wise 1980; Wise and Rompre 1989; Gardner 1992). Different substances may have different mechanisms of activating or influencing dopaminergic systems. A variety of neurotransmitter systems such as serotonergic, adrenergic, and gamma-aminobutyric acid (GABA)-ergic are involved in regulating motivated behavior and thereby are also linked to the reinforcement effects of drugs (Jaffe 1990).

Conditioned responses following alcohol or other drug use develop in response to environmental cues such as certain people, places, or objects. Activation of conditioned responses may produce craving. Craving and the mechanisms regulating craving are not well understood, especially in adolescents, but they involve an association between reward centers and memory centers located in the hippocampus within the limbic system (Wise and Rompre 1989; Gardner 1992). The user associates specific cues or stimuli with prior experience of drug-induced positive or negative reinforcement. Craving may follow as an emotional-motivational anticipatory response to potential reinforcement. Craving may be an underappreciated phenomenon in adolescents; however, it is a central component of the dependence syndrome (Edwards and Gross 1976). A significant percentage of adolescents who meet criteria for alcohol dependence report craving (Martin et al. 1995).

NEUROPSYCHIATRIC EFFECTS OF SUBSTANCE USE

Acute Effects

Although specific neuropsychiatric effects of psychoactive substances are due to neuropharmacological changes, numerous factors can modify both the effect of the substance and the experience of the user (Bukstein and Tarter 1998). Drug dose is, of course, an important determining factor on acute effects. Dose is multifaceted and, in naturalistic settings, often difficult to ascertain. Quantity and purity synergistically determine the person's response from both a pharmacological and a neuropsychiatric perspective. Adolescents are more likely than adults to be

novice or inexperienced in the use of specific substances and their simultaneous combinations (e.g., alcohol and tobacco). They may be unknowledgeable about the substance that they are consuming, a safe dose, and the level of change or impairment produced by specific substances. Due, in part, to inexperience, the manifestation of pronounced effects may precipitate an extreme level of distress, particularly agitation and anxiety. These reactive dysphoric states may compound the direct neuropharmacological effects of a drug use episode. Adolescent inexperience may also result in risky behaviors in potentially dangerous situations as the adolescent confronts social and developmental challenges common to youth.

Expectancies and the social context of use are also important modifiers of the pharmacological actions that culminate in mood, cognitive, and behavioral changes (Christiansen et al. 1982). Among adolescents, expectations of the effects of substance consumption are different from adults. These expectancies may regulate whether an adolescent decides to initiate consumption. Without knowledge or prior experience, these expectancies can be both incorrect and maladaptive. With respect to inaccuracy, adolescents may believe that alcohol is an aphrodisiac or an analgesic. Furthermore, expectancies regarding substance use can impose personal risk. For example, disinhibition as manifested by “falling down drunk” may be seen as a goal of drinking among adolescents rather than a negative consequence to avoid. Deviant social behavior while under drug influence (e.g., aggressive behavior) may also be more acceptable in certain adolescent populations. Thus, expectancies about the effects of drugs, and the behaviors tolerated while under acute influence, moderate the neuropharmacological effects (Bukstein and Tarter 1998).

Not every intoxication episode is pathological, that is, producing maladaptive changes. Among adolescents, many episodes are not accompanied by negative consequences, especially emotional or behavioral sequelae. Adolescents commonly display a different pattern of substance use behavior compared to adults. Alcohol consumption is typically expressed as a binge pattern rather than persistent and continuous drinking (Martin et al. 1993).

The neuropsychiatric effects of the various compounds are determined largely by the neuropharmacological properties of the compound. Amphetamines and other stimulants exert their actions by releasing dopamine and norepinephrine from the presynaptic neuron and block their reuptake by the presynaptic neuron. The net result is greater availability of neurotransmitter in the synapse. Stimulant action on dopaminergic neurons in the mesolimbic area thus produces mood changes, while action in the mesocortical cortex impacts on higher cognitive processes.

LSD acts primarily on the serotonin system, having both inhibitory and excitatory effects. Alcohol and other sedative/hypnotic compounds affect several neurotransmitter systems. Action on GABA (a major inhibitory neurotransmitter) receptors may be involved in alcohol-induced, anxiolytic responses. Simulta-

neously, alcohol's effects on the dopaminergic and serotonergic systems likely impact on its reinforcing properties (Tabakoff and Hoffman 1987, 1992). Opiates stimulate endogenous opiate receptors, resulting in permanent changes in receptor function (Koop and Bloom 1988).

Acute Neuropsychiatric Effects

Adolescents commonly display a different pattern of substance use behavior compared to adults. Alcohol consumption is typically expressed as a binge pattern rather than persistent and continuous drinking (Martin et al. 1993). Intoxication, depending on the specific substance, produces an array of neuropsychiatric effects involving alteration of perception, thought processes, mood/affect, and behavior (Bukstein 1995; Bukstein and Tarter 1998).

Alcohol

Low-dose alcohol use affects perception by impairing visual motor abilities and dulling of pain perception. Higher doses produce greater effects on these processes. Abnormalities in thought processes include impaired judgment, concentration, and recent memory beginning at lower doses and disorganized thinking, confusion, and progression to stupor and coma at progressively higher doses. Effects on mood and affect consist of initial excitement, relaxation, and occasional irritability. Later, depressed mood is more common as blood alcohol levels drop. At higher doses, users may experience low frustration tolerance and more dramatic mood swings.

Cannabis (Marijuana)

Common perceptual effects of marijuana include a greater sensitivity to stimuli and, at higher doses, altered self-image, depersonalization, anesthesia, pseudohallucinations involving various sensory processes, and frank visual hallucinations. Thought processes are affected by impaired judgment and deficits in short-term memory, attention span, and information processing. At higher doses, thoughts can become fragmented with resulting confusion, delusions, paranoia, and delirium. Effects on mood and affect commonly consist of euphoria, relaxation, and a sense of well-being. Some individuals can experience anxiety and panic attacks, especially at higher doses. Behavioral effects include sedation, impaired motor coordination, disinhibition, and impaired ability to perform complex motor tasks at lower doses and simple tasks at higher doses.

Cocaine and Other Stimulants

Perceptual disturbances due to cocaine or other stimulant (e.g., amphetamines, methylphenidate) use are more common at higher doses and include perceptual distortions, pseudohallucinations such as abnormal tactile perceptions, and hallu-

cinations. Low-dose stimulants can improve concentration, attention, and task persistence, although the use of high doses may result in psychosis, paranoia, and coma. Effects on mood and affect consist of a sudden euphoria or “rush” as well as increased energy, although dysphoria (irritability or depression) and anxiety or panic may be increasingly more common. As the effects of cocaine or stimulant intoxication wear off, the user may experience a period of intense dysphoria or a “crash.” The user may appear restless and increasingly excited and activated. Impulsivity, agitation, and aggression may also result from higher doses.

Opiates

Perceptual effects consist primarily of analgesia and a general dulled response to external stimuli. The user often experiences mental clouding and impaired concentration and attention, even at lower doses, while stupor and coma may result from higher doses. Effects on mood and affect may include euphoria, relaxation, a “rush” (if intravenous or intranasal ingestion), or giddiness. The user may appear sedated or apathetic with motor incoordination and slurred speech.

Sedative/Hypnotics

Sedative/hypnotic use produces relaxation, a calming effect, and occasionally euphoria. Higher doses may result in mood swings and depression. Impairment in thought processes includes deficits in attention, concentration and memory progressing to confusion, stupor, and coma at higher doses. Behavioral effects consist of sedation, motor incoordination, disinhibition, and slurred speech.

Hallucinogens

The primary psychotropic effects of this class of substances are perceptual abnormalities, which include visual hallucinations, time and space distortions, anesthesia and sensory overflow, depersonalization, and derealization. Postuse, the user may experience “flashbacks” consisting of intensification of perceived stimuli, perception of motion of fixed objects, and geometric patterns superimposed on the field of vision. Short-term memory and concentration are often impaired. The user may experience apparent important insights post use that are later recognized as not being particularly insightful. Effects on mood and affect can include anxiety and fearfulness, which may progress to panic and dysphoria or a “bad trip.” Behaviorally, the user may experience withdrawal and be hypervigilant.

Inhalants

The behavioral effects of inhalants consist of disinhibition, slurred speech, and motor incoordination and sometimes impulsive, bizarre behavior at higher doses. Mood or affect can be variable, ranging from euphoric to dysphoric. Judgment is often impaired. Perceptual effects consist of dizziness, anesthesia, disassociation,

distortion of size, shapes, and time, abnormal sensitivity to light, double vision, and ringing in the ears. At higher doses hallucinations are possible. Inhalant use can impair judgment and produce a toxic psychosis or delirium at higher doses.

Anabolic Steroids

A number of adverse behavioral effects including aggressiveness, irritability, hostility, anger, and impaired judgment have been reported with the use of anabolic steroids, which are often used by body builders. In addition to increased male secondary sex characteristics, females can also show such behavioral effects. Even several days of use of such anabolic steroids as methyltestosterone can produce negative mood states, mood swings, violent feelings, and hostility.

Tobacco (Nicotine)

Nicotine use results in relaxation and improved reaction time and attention at lower doses that are typical of normal exposure.

Chronic Neuropsychiatric Effects

A considerable literature has developed documenting the neuropsychiatric sequelae of alcohol and other substance use among adults (Parsons 1993; Fals-Stewart et al. 1994). In contrast, there is a paucity of research examining the chronic or long-term sequelae of substance use and abuse among adolescents. These compounds have strong neuropharmacological effects while the brain of the adolescent is still undergoing brain maturation in tandem with physical, psychological, and endocrinological maturation (Lewis and Volkmar 1990; Rutter and Rutter 1993).

Alcohol, opiates, and sedative/hypnotics have individual dependence or withdrawal syndromes associated with chronic use. Psychosis can result from the use of cocaine or other stimulants, as well as cannabis/marijuana. Anxiety appears to be commonly associated with cocaine and other stimulant and marijuana use. Despite ample evidence demonstrating neuropsychiatric effects of substance use and associated transient psychiatric symptoms upon acute intoxication, there is little evidence that substance use or abuse directly causes persistent psychiatric syndromes (Bukstein et al. 1989).

Externalizing or disruptive behavior disorders (e.g., attention-deficit hyperactivity disorder, conduct disorder, oppositional, defiant disorder) or delinquency almost always precede substance use (Loeber 1988). Depressive disorders among adolescents have been shown to emerge following the onset of substance use disorder; however, the natural history of adolescent comorbid mood substance use disorders appear to have a different pattern from that observed in most adults (Bukstein et al. 1992; Riggs et al. 1995). Whereas depressive symptoms in adults with substance use disorders commonly remit rapidly with abstinence (Bukstein

et al. 1989), a substantial proportion of adolescents with comorbidity continue to display depressive symptoms after several weeks of abstinence. This finding suggests that there may be a predisposition to affective disorders in substance-abusing adolescents, which, once manifest, are less responsive to abstinence. Although in adults the rapid amelioration of depressive symptoms suggests a direct etiological role of psychoactive substance use on mood (Schuckit 1986), the lack of a similar abstinence response in many adolescents suggests that depressive symptoms may have a different etiological mechanism apart from the direct acute or chronic effects of substance use.

Substance use disorder among adolescents is a risk factor for suicidal behavior, including ideation, attempts, and completed suicide (Crumley 1990). Possible mechanisms for this relationship include acute and chronic effects of psychoactive substances. Adolescent suicide victims are frequently using alcohol or other drugs at the time of suicide (Friedman 1985; Brent et al. 1987). One acute effect of a substance is to produce a transient and intense dysphoric state, disinhibition, impaired judgment, and increased level of impulsivity. Drug use may also exacerbate preexisting psychopathology, including depression or anxiety disorders, which may place the adolescent at risk for suicidal behavior (Schuckit 1986; Brent and Kolko 1990; Bukstein 1994). Comorbidity, especially mood disorders with other nonmood disorders such as substance use disorders, is one of several putative risk factors for completed suicide (Brent et al. 1988; Bukstein et al. 1993).

Anxiety disorders are also frequently present in adolescents with SUDs. Generalized anxiety disorder and panic disorder may be consequences of chronic use (Kushner et al. 1990). Similar to the findings in adults, adolescents in treatment present high rates of social phobia and posttraumatic stress disorder (Clark et al. 1995). However, panic disorder and generalized anxiety disorder appear to be rare among adolescents seeking treatment for alcohol abuse or dependence (Clark et al. 1995). These latter findings are consistent with the hypothesis that social phobia is more likely to precede alcohol dependence and is consistent with the hypothesis that substance use initiation is for these individuals an attempt to self-medicate this disorder.

Aggressive behaviors are present in many adolescents who have substance use disorders (Milan et al. 1991; Bukstein 1994). Consumption of abusable substances such as alcohol, amphetamines, and phencyclidine increases the likelihood of aggressive behavior (Moss and Tarter 1993). The direct pharmacological effects may be exacerbated by the presence of preexisting psychopathology, the use of multiple agents simultaneously, and the relative inexperience of the adolescent substance user. Early aggressive behavior predicts subsequent substance abuse (Robins 1966; Kandel et al. 1978); serious aggressive behavior precedes severe involvement with drugs (Johnston et al. 1978). Chronic aggressive behavior among adolescents is often associated with a diagnosis of conduct disorder,

which almost always precedes substance use (Loeber 1990, 1991). Individuals with suicidal and/or aggressive behavior share certain biochemical characteristics such as deficits in noradrenergic, serotonin, and GABA/benzodiazepine systems (Eichelman 1987). Each of these neurotransmitter systems can be affected by psychoactive substances as well as have a role in the pathogenesis of several psychiatric disorders. Among adult aggressive and impulsive offenders, investigators have found very high rates of early onset substance abuse, suicidal behavior, and low-serotonin metabolites (Roy and Linnoila 1986; Buydens-Branchey 1989; Linnoila et al. 1989).

Despite the acute and chronic effects of psychoactive substances on neurotransmitter systems, abnormalities of these neurotransmitter systems may precede the development of substance use disorders. The contribution of such biochemical abnormalities toward increased risk may proceed through a number of possible mechanisms. For example, serotonergic deficits may underlie impulsive and aggressive behavior and poor mood regulation as well as predispose to specific psychiatric diagnoses. These psychiatric problems may lead to an increased risk for the development of substance use disorders. In addition to problems with aggression, impulsivity, and mood, neurotransmitter abnormalities may be manifested as sensitized brain reinforcement produced by various psychoactive substances, thus promoting the risk for a behavioral pattern leading to substance dependence.

Psychiatric disorders in childhood, featured by disruptive behavior disorders as well as mood or anxiety disorders, confer an increased risk for the development of substance use disorders in adolescence (Christie et al. 1988; Loeber 1988; Bukstein et al. 1989). The etiological mechanisms have not, however, been systematically researched. Within a general pattern of deviancy, alcohol and drug consumption can be considered as part of a nonnormative lifestyle. Following an internalizing type of disorder (e.g., anxiety, depression), substances have obvious short-term benefits of reducing negative or aversive mood states. Hence, there are many factors, including classical conditioning principles, that interact to predispose to substance use initiation and maintenance.

TREATMENT STRATEGIES

Pharmacotherapy can be used to target a variety of specific clinical situations that present during the treatment of an adolescent with a substance use disorder. The ample evidence pointing to the role of neuropsychiatric factors in the etiology and development of SUDs in adolescents supports serious consideration of pharmacological strategies in SUD treatment. Despite the substantial pharmacological treatment literature for adults, the empirical basis for the pharmacological treatment of adolescents is sparse and underdeveloped (Solhkhah and Wilens 1998; Bukstein and Tarter 1998). While this situation mirrors the paucity of empirically based psychosocial treatments for adolescents versus the many interventions es-

established for adults, there are many reasons for research and the development of adolescent SUD treatments to trail the adult literature: (1) there is a general trend for novel treatments to be initially tested in adults and then, later, to be adapted and tested in adolescent populations; (2) similar to the initial reluctance to use medications for adults with SUDs, there may be a greater reluctance to do so for adolescents; (3) the general denial of parents to recognize the presence or severity of SUDs in their offspring may limit their enthusiasm for a seemingly intrusive intervention such as medication; (4) the frequent denial and poor compliance of the adolescents themselves may limit valid tests of the efficacy of specific medications; (5) the number of investigators qualified to conduct such trials is limited; (6) the field of adolescent psychopharmacology is generally a nascent area. Few empirically based pharmacological treatments exist for adolescents with noncomorbid disorders such as major depressive disorder (MDD), bipolar disorder, anxiety disorders, and even ADHD. Despite the common occurrence of psychiatric comorbidities in clinical populations of adolescents, there is a reluctance to test pharmacotherapies in comorbid populations prior to more definitive work with adolescents having single disorders.

Common pharmacotherapeutic strategies consist of treating withdrawal symptoms, substitution therapy (e.g., replacing heroin with methadone), craving reduction along with blocking strategies (i.e., using naltrexone for treatment of alcoholism), and aversive therapy (i.e., using disulfiram to maintain alcohol abstinence (Solikhah and Wilens 1998; Kranzler et al. 1999). This list can be further expanded to include comorbid psychiatric conditions that lead to early use or contribute to continued use. The limited research literature on the use of pharmacotherapies with adolescents necessitates the guidance of the adult literature on the use of pharmacological agents to assist the clinician in the most supported approaches for adolescents. While some pharmacological therapies have empirical support for their use in adolescents, the use of medications should always be part of a multimodal treatment approach. A number of psychosocial treatment approaches have been shown to be effective, including several models of family therapy and several types of patient-centered approaches such as peer group therapy, cognitive-behavioral interventions, problem-solving training, and relapse prevention (Weinberg et al. 1998). Williams and colleagues' (Williams and Chang 2000) more recent review of adolescent treatment outcome in 53 studies reported that there was evidence that treatment was superior to no treatment. Although insufficient evidence was found to compare the effectiveness of treatment modalities, outpatient family therapy appeared to be superior to other forms of outpatient treatment.

Withdrawal

The existing literature (Vingilis and Smart 1981; Martin et al. 1995) suggests that adolescent subjects experience fewer symptoms of physiological withdrawal.

Withdrawal symptoms in animal models support this. For example, a study by Acheson and colleagues (1999) used an animal model that induced seizures in adolescent and adult rats pretreated with high levels of alcohol and found that the adolescent rats showed fewer symptoms of withdrawal. No controlled studies of alcohol and drug withdrawal in the adolescent population are available, and this perceived or real lack in the severity of withdrawal or frequency of symptoms may be one of the reasons why. Currently, adolescents experiencing clinically significant withdrawal symptoms are treated using adult guidelines, and the reader is referred to several guidelines and reviews for a detailed review of the clinical management of substance withdrawal (APA 1995; NIH 1998; Claasen and Adinoff 1999). Even though adolescent drug abusers may experience fewer symptoms of withdrawal, every effort should be made to evaluate them for past symptoms of withdrawal along with amount, frequency, and duration of current use.

Substitution Therapy

The goal behind substitution therapy is to replace an addictive harmful substance with another substance that prevents symptoms of withdrawal along with functional impairment. Substitution therapy is a common yet controversial strategy for treating adults with opiate addiction. Treatment consists of either methadone or levo- α -acetyl methadone (LAAM), a longer-acting opiate. The goals of treatment are to prevent withdrawal, eliminate drug craving, and block the euphoric effects of illicit opiate use (Kaminer 1995). Adolescent opiate abusers should be admitted to methadone maintenance treatment programs only if state or local laws or regulations allow, an adult gives written consent, and there are at least two failed attempts at short-term detoxification or drug-free treatment (Kaminer 1995). Each attempt should be separated by at least one week and the medical record must be well documented to show continued physiological addiction to opiates. Given the above, other substitution treatments are being sought. One promising drug is buprenorphine, which is an opiate agonist/antagonist, that can be prescribed in the outpatient office. It has shown efficacy in the treatment of opiate dependence (NIDA 2000). However, there are no controlled trials or case studies for the use of buprenorphine in adolescents.

Tobacco Cessation

The pharmacological treatment of tobacco cessation largely involves substitution therapy or nicotine replacement. Tobacco-dependant adolescents manifest the similar types and severity of withdrawal symptoms as adults (Rojas et al. 1998; Moolch and Henningfield 2000). In studies of adult smokers, nicotine-replacement therapy has been shown to increase cessation rates over placebo (Hughes et al. 1999). In the single published study of an 8-week open-label trial of nicotine-

replacement therapy (patch) in adolescents, Smith and colleagues (1996) reported that only 1 of 22 adolescents remained abstinent after 6 months.

Nicotine substitution is *not* contraindicated in adolescents, and given the significant health risk from smoking, adolescents should be permitted treatment. However, an adolescent must be supervised during therapy and motivated for treatment (AACAP 1998). Nicotine preparations are available in various forms: transdermal patch, inhaler, gum, and nasal spray. Side effects can be expected. For example, most smokers using the nasal spray experience throat irritation, rhinitis, sneezing, coughing, and lacrimation during the first week of therapy (Hughes 2000). The inhaler can cause similar side effects. Possible side effects with the gum include mouth irritation, gastrointestinal symptoms, insomnia, dizziness, and headache (Micromedex[®], 2000). The patch can cause skin irritation and tachycardia. The adolescent must be given strict guidance not to smoke while on nicotine since this may cause nicotine intoxication that generally consist of nausea, vomiting, abdominal pain, and increased salivation (Micromedex[®], 2000). Length of therapy varies on the degree of addiction.

Bupropion (Wellbutrin[®]), an atypical antidepressant, also shows significant promise when treating nicotine addiction since it doubles quit rates (Hughes 2000). Its success is not linked to treatment of depression in smokers since it has proved efficacious in people without any current or past symptoms of depression (Hughes 2000). Side effects can consist of nausea, vomiting, seizures, tremors, agitation, insomnia, and hypersensitivity reaction (Micromedex[®] 2000). Patients should be questioned about seizure and eating disorders since increased risk of seizure may result. Bupropion is commonly used in adolescent patients for treatment of depression, but no guidelines are available for dosing bupropion in adolescents who desire to quit smoking.

The most salient issue of using substitution therapies with adolescents involves motivation, as adolescents often do not recognize their use patterns as problematic. For tobacco smoking, motivational interviewing techniques have demonstrated preliminary success in affecting smoking cessation among adolescents (Colby et al. 1998). Pharmacotherapies should be combined with psychosocial interventions such as psychoeducation, motivational enhancement, or cognitive-behavioral therapy (Moolchan et al. 2000).

Craving Reduction and Blocking Strategies

Various strategies have been employed to decrease craving that is the urge or desire to use a particular drug or to block the positive reinforcing qualities of a drug. Naltrexone (ReVia[®]), the most prominent example, reduces the positive reinforcing pleasurable effects of alcohol as well as its craving (Swift 1999). As a result, alcohol consumption can be reduced and abstinence prolonged. Naltrexone's potential effectiveness within the adolescent population has been demon-

strated by several case reports. In one case report, Wold and associates (Wold and Kaminer 1997) treated an adolescent with alcohol craving and showed a favorable response with naltrexone at 50 mg per day. This adolescent also had comorbid marijuana dependence and symptoms of conduct disorder. In another case report, Lifrak and colleagues (1997) showed that naltrexone reduced alcohol craving in two adolescents during a 12-week course of treatment, and one adolescent maintained abstinence for several weeks following therapy. No controlled trial using naltrexone for the treatment of alcohol dependence in adolescents has been conducted.

Naltrexone is also used in opiate addiction to lessen craving and prolong recovery periods; however, the adolescent literature is without case studies or controlled trials of its use with opiate dependence. Naltrexone side effects include nausea, headache, dizziness, and anxiety (Micromedex® 2000).

Opiate and cocaine craving have also been treated by pharmacotherapeutic interventions. In the adult literature, buprenorphine, an opiate agonist/antagonist, has been successful in treating opiate abuse (NIDA 2000). Recent reviews have stated that buprenorphine carries less risk of overdose given its agonist/antagonist mechanism of action (NIDA 2000); however, a paper by Reynaud and associates (1998) reported the possibility of six deaths secondary to the concomitant use of buprenorphine and benzodiazepines. Buprenorphine side effects consist of nausea, vomiting, hypotension, and sedation. (Micromedex® 2000). No controlled studies or case reports for buprenorphine are available for adolescent opiate abusers.

The pharmacotherapy of cocaine craving has been addressed in the adolescent literature via three case reports by Kaminer (1992a,b). Desipramine was used and was successful in one adolescent with cocaine dependence, major depression, and ADHD. In the other two case studies, one was successful and the other dropped out of treatment. The current literature is without additional case studies or controlled trials to support the efficacy of tricyclic antidepressant (TCA) use in the treatment of adolescent cocaine abusers.

Aversive Therapy

Aversive interventions are used to reduce or eliminate the craving or desire for alcohol or other drugs (Bukstein 1995). One of the most common and controversial forms of aversive therapy is disulfiram (Antabuse®). Disulfiram's use in treating alcoholism began in 1948 (Myers et al. 1995). It works by inhibiting the action of aldehyde dehydrogenase, and this in turn causes an increase in acetaldehyde that produces a potent noxious reaction in the person who decides to drink alcohol while taking it. Disulfiram works within minutes of a person taking a drink and produces the following side effects: facial flushing, sweating, nausea, vomiting, headache, dyspnea, weakness, dizziness, blurred vision, and confusion

(Janicak et al. 1997). In rare cases it causes respiratory depression, shock, arrhythmias, seizures, and death (Janicak et al. 1997). Also, reports of psychotic reactions, neuropathy, blurred vision, seizures, and hepatitis are documented (Micro-medex 2000). A host of drug-drug interactions exist. There are no published controlled trails of disulfiram in adolescents. Given the potential problems, disulfiram should be a treatment of last resort in an adolescent suffering from an alcohol use disorder. This may be why there are no controlled trials. Limited case reports are available. Myers and colleagues (1995) published a case study involving two adolescent males afflicted with alcohol dependence. One youth remained abstinent for a prolonged period while the other was noncompliant and relapsed. Of course, many concerns can be raised about the use of disulfiram in this population given issues of noncompliance, impulsiveness, and questionable motivation. In order for disulfiram to be a realistic treatment option, the adolescent must be supervised in taking it and must also be medically healthy, intellectually competent, insightful about his or her drug use, and highly motivated for recovery (Solikhah and Wilens 1998).

TREATMENT OF COMORBID PSYCHIATRIC DISORDERS

The presence of large numbers of youth with comorbid psychopathology in clinical samples of adolescents with SUDs suggests that treatments that have previously been directed toward children and adolescents with comorbid psychopathology, particularly medications, may be useful in the treatment of adolescents with SUDs and comorbid psychopathology.

Depression and Mood Disorders

The treatment of depression in adults with alcohol dependence has received much attention in the literature. In a double-blind, placebo-controlled study of an selective serotonin-reuptake inhibitor (SSRI) antidepressant (fluoxetine) in adult depressed alcoholics, Cornelius and colleagues (1997) reported efficacy for fluoxetine versus placebo in treating both the depression and the drinking of adult alcoholics with comorbid major depressive disorder. Studies using SSRIs in mostly non depressed adults have had more equivocal results (Kranzler et al. 1995), suggesting that treating the comorbid psychiatric disorder or problem may be the mechanism for improvement rather than the action of the agent on the alcohol use disorder (AUD) per se.

Two published studies have evaluated the efficacy of fluoxetine or any other SSRI antidepressant in adolescents with substance dependence. Riggs and colleagues (1997) conducted an open-label trial involving eight male adolescent subjects who were treated with a 20 mg dose of fluoxetine for 7 weeks. These subjects displayed either cannabis abuse or cannabis dependence and conduct

disorder in addition to an alcohol use disorder and major depressive disorder. Of the eight adolescents, seven demonstrated marked improvement in depressive symptoms and wished to continue on fluoxetine after the trial. Significant within-group improvement in depression was noted on the Clinical Global Impression (CGI) scale, as well as on observer-rated and self-rated measures of depressive symptoms. As the study was conducted in the controlled environment of a residential treatment center, the efficacy of fluoxetine for treating alcohol or substance use could not be assessed. No serious side effects were noted during the trial, and no patient was discontinued from the medication because of side effects. Cornelius and associates (2000) conducted a 12-week open-label study of fluoxetine in an outpatient setting with 13 adolescents diagnosed with comorbid AUD and MDD. The study found a significant within-group decrease (improvement) for both depressive symptoms and drinking. The fluoxetine was well tolerated.

Given the absence of evidence establishing the effectiveness of TCAs in adolescents and the potential of adverse events and interactions with substances of abuse (Wilens et al. 1997), the use of TCAs in adolescents with SUDs should be avoided whenever possible. Similarly, the use of monoamine oxidase inhibitors (MAOIs) presents problems due to adolescent impulsivity and potential interactions with various foods and medications or substances of abuse (e.g., opiates or stimulants).

Bipolar Disorder

In perhaps the only published double-blind placebo-controlled trial in adolescents with SUD, Geller and colleagues (1998) conducted a 6-week study of 25 adolescents, aged 12–18 years, who were randomly assigned to receive either placebo or lithium carbonate. Using both intent-to-treat and completer analyses, there were significant differences on continuous and categorical measures between the lithium and the placebo groups for both psychopathology measures and weekly random urine drug screens. The use of other mood stabilizers such as valproic acid and carbamazepine is suggested by several case studies in adolescents with bipolar disorder alone.

ADHD

Psychostimulant medications, which include methylphenidate, dextroamphetamine, and pemoline, have been shown to effectively treat ADHD (Barkley et al. 1990). While there are many studies of treatment for children with ADHD (Swanson et al. 1995; Spencer et al. 1996), there only a few dozen published studies of stimulant treatment with adolescents and very few controlled studies. Although studies of the stimulant treatment of adolescents show improvement in ADHD symptoms and, often, in global functioning (Klorman et al. 1987; Pelham et al. 1991), the effect sizes in adolescent studies are smaller than those

estimated in studies with other children (Klorman et al. 1987; Pelham et al. 1991; Smith et al. 1998). One recent study found comparable effect sizes in both adolescents and children if administration and similar activities are evaluated as dependent measures of effectiveness (Smith et al. 1998). If stimulants are or appear to be less effective in adolescents, reasons for this finding may include a number of environmental variables such as poorer compliance or an increased presence of comorbid psychopathology in adolescents with ADHD, especially SUDs/SUDs (Smith et al. 1998).

Psychostimulants, such as methylphenidate and dextroamphetamine, while among the most studied and effective of medications in youth with ADHD, present a number of potential problems for use in populations of adolescents with SUDs. Despite their potential for effectively treating ADHD, there are several limitations to the use of stimulants. Stimulants cannot be easily used late in the day or evening, and they may have adverse effects on mood (Barkley et al. 1990). Methylphenidate and dextroamphetamine are classified as Schedule II by the U.S. Drug Enforcement Administration (DEA), thus indicating a high potential for abuse (Jaffe 1991; DEA 1995; Riggs 1998). Despite their efficacy in the treatment of ADHD, methylphenidate and dextroamphetamine have not been studied in the treatment of adolescents with SUDs and ADHD. While the use of stimulant medication for ADHD symptoms in adolescents is empirically supported (Smith et al. 1998), as it is for children with ADHD in general (MTA 1999), controversy remains regarding stimulant medication use among adolescents with substance use-related problems. Two studies have shown an association between decreased substance use disorder and use of stimulant medication for adolescents with ADHD (Biederman et al. 1999; Molina et al. 1999), but concerns still remain about the appropriate use or possible misuse of stimulant medication by adolescents with conjoint substance abuse and ADHD problems.

Pemoline, another CNS stimulant and a Schedule IV medication, has a lower abuse potential as supported by animal and human studies (Langer et al. 1986; Riggs et al. 1996). Riggs and colleagues (1996) conducted a one-month open trial of pemoline in 13 adolescents, ages 14–18, with SUD, ADHD and CD who were being treated in a residential drug and alcohol treatment center. After one month of pemoline treatment, mean Conners Hyperactivity Index scores and physical activity scores decreased from baseline. Concerns about hepatic toxicity raised concerns about its use as a first-line drug (FDA 1997).

Given the potential risks (as described above) of prescribing stimulant medications to substance-abusing youth, alternatives to stimulants need to be studied for this population of adolescents with ADHD. A number of antidepressants such as TCAs (Rapoport et al. 1974; Saul 1985; Biederman et al. 1989) and bupropion (Barrickman et al. 1995) have shown efficacy in the treatment of ADHD. The use of TCAs in the treatment of ADHD may pose several limitations including reports of tolerance after initial improvement (Waizer et al. 1974; Quinn and

Rapoport 1975) and potential cardiovascular system toxicity and reactions (Riddle et al. 1993; Alderton 1995; Varley and McClellan 1997).

The similarity between some tricyclic and heterocyclic antidepressants and bupropion in their effects on monoamine reuptake has prompted several investigations into the efficacy of bupropion for ADHD. Bupropion is a noradrenergic and dopamine reuptake blocker that is in current use as an antidepressant (Davidson and Connor 1998). It has a low side effect profile with low cardiotoxicity (Ferris et al. 1983). A newer preparation, bupropion sustained release (SR), is an attractive candidate agent for the treatment of comorbid ADHD and AUD/SUDs for several reasons. First, its status as an indirect dopamine agonist and enhancer of norepinephrine bioavailability (Pliska et al. 1996) makes it a possible agent for ADHD, in which both noradrenergic and dopaminergic mechanisms are involved (Spencer et al. 1996; Pliska et al. 1996). Second, dopaminergic mechanisms in the nucleus accumbens have been implicated in the development of SUDs. Bupropion may also have an effect on aggression in youth with ADHD (Connors et al. 1996). Bupropion appears to have low abuse potential on physiological measures compared with dextroamphetamine (Griffith et al. 1983). Bupropion also has few adverse effects (Settle 1998).

Approval by the U.S. Food and Drug Administration (FDA) for the use of bupropion for smoking cessation and its efficacy in controlled clinical trials (Settle 1998; Goldstein 1998) suggests the potential value of this agent for addictive disorders. The development of nicotine dependence may be related to nicotine's stimulatory effects on the dopaminergic pathways in the mesolimbic system, which are also implicated in the development of dependence of other substances of abuse (Pontieri et al. 1996). There have been several trials of bupropion in adults with SUDs. Margolin and associates (1991), in an open trial of bupropion in cocaine addicts on methadone maintenance, found reports of reduced cocaine craving. In a placebo-controlled randomized double-blind clinical trial in the same population (Margolin et al. 1995), depressed subjects receiving bupropion had a statistically significant decrease in positive urine screens for cocaine.

There are a number of studies of bupropion in various populations of children, adolescents, and adults with ADHD. Connors and colleagues (1996) conducted a placebo-controlled, double-blind study of children 6–12 years old with ADHD. In the 1996 Connors et al. report of two colleagues at other sites (Casat et al. 1987, 1989; Clay et al. 1988), bupropion showed significant improvements over placebo in various measures of global improvement, including lower hyperactivity and improved aggression within children with aggression. Barrickman and associates (1995), in a double-blind crossover study comparing bupropion and methylphenidate in 15 subjects 7–17 years old (mean age 11.8 years) with ADHD, reported significant improvements over baseline in both parent and teacher reports and clinical global impression (CGI). No significant differences between treatments were noted, although almost all the measures appeared to

favor methylphenidate. Existing treatment studies of ADHD using bupropion are limited by their small sample sizes (maximum 15 patients).

The only study that has examined the use of bupropion in subjects with both ADHD and SUDs is by Riggs and associates (1988)—a 5-week open trial of bupropion in 13 nondepressed adolescent boys, ages 14–17 (mean = 15.5) years, in a residential treatment facility. These adolescents had comorbid diagnoses of SUD, ADHD, and CD. The investigator's titrated immediate release bupropion to a maximum of 300 mg/day in three doses. By the fifth week, the subjects' mean scores on the Conner's Hyperactivity Index, the Daydream Attention Scores, and CGI showed significant improvement over baseline. Because the study was conducted in the controlled environment of a residential treatment center, the efficacy of bupropion for treating alcohol or substance use could not be assessed.

The clinical management of the adolescent with comorbid SUD and ADHD is a challenging task, as the results will help determine the ultimate success in controlling the range of academic and social dysfunction that often accompanies this form of comorbidity. Psychosocial interventions such as family therapy, targeting parenting practices, and cognitive-behavioral approaches are an essential background to medication decisions. Nonstimulant options should be thoroughly considered. If a stimulant is necessary to produce clinically significant results, close supervision of administration by responsible adults is critical. The choice of a long-acting stimulant is preferred. Newer agents such as OROS[®] methylphenidate (Concerta[®]) may have lower abuse potential owing to their long duration of action and novel delivery system that does not allow crushing (and nasal ingestion).

Aggressive Behavior

The frequent comorbidity of SUDs and conduct disorder, particularly with aggressive behavior, suggests that targeting aggression or severe agitation is a common pharmacological management concern (Moss and Tarter 1993). The use of other agents, such as antidepressants, mood stabilizers, α -adrenergic agents (e.g., clonidine), and neuroleptic agents, for the treatment of aggression in adolescents with SUDs is much less established, with only several case reports, open drug trials, and a limited treatment literature for use in youth with SUDs. Much of the use of these medication classes and research has been for aggressive or acutely agitated youth without SUDs (Bukstein 1994; Karper and Krystal 1997). Acute treatment of aggressive or agitated behavior should insure the safety of the adolescent and those in his or her environment. Ideally, the clinician should be aware of the substances being used. Antipsychotics used with certain drugs, such as phencyclidine (PCP), can result in adverse events such as cardiovascular complications. While carrying a risk of disinhibition and abuse if used in long-term

treatment, benzodiazepines may be used acutely. The clinician should be cautious that the adolescent's behavior is not complex drug-seeking behavior.

Long-term treatment follows guidelines used for aggressive adolescents in general, targeting comorbid disorders such as MDD or bipolar disorder with appropriate agents such as SSRIs or mood stabilizers. Specific targeting of aggression/agitation alone during long-term treatment should consider the potential abuse of the agent used as well as potential interactions with likely substances of abuse.

Psychosis

The common acute substance-induced neuropsychiatric sequelae of psychosis suggest a careful evaluation of the adolescent's recent substance use history. Treatment should be commenced using the lowest effective dose of antipsychotics in these patients and using as-needed (prn) doses as necessary in addition to regular doses. When the psychosis resolves, tapering of the antipsychotic should be instituted. If the psychosis does not resolve and it is determined that the patient has an underlying psychiatric disorder accounting for the psychotic symptoms, it is important to accurately delineate the specific psychiatric condition, i.e., depression, bipolar disorder, schizophrenia, etc., and use appropriate medication strategies such as mood stabilizers and anitidepressants.

LIMITATIONS OF PREVIOUS STUDIES OF PHARMACOTHERAPY WITH ADOLESCENTS WITH SUDs AND COMORBID PSYCHOPATHOLOGY

There are few published well-designed, controlled trials of medication treatment in populations of adolescents with SUDs or SUDs and comorbid ADHD. Geller et al.'s (1998) double-blind placebo-controlled study of lithium carbonate remains the only controlled medication trial in this population. Only two published studies were found dealing with the stimulant or other medication treatment of adolescents with ADHD and SUDs (Riggs et al. 1996, 1998). These studies, like that of Riggs and associate's study of fluoxetine for MDD, are limited by the location in a residential treatment facility, where substance use may be limited and therefore measures of alcohol or other substance use may not be relevant. Additional limitations of existing studies include their low sample size, absence of controls, short duration (1 month to 5 weeks), inclusion of only males, and limited evaluation of the effects of bupropion on alcohol and substance use as well as other behaviors and symptoms.

SAFETY AND COMPLIANCE

The potential concurrent use of psychotropic agents with substances of abuse raises salient questions about the safe use of these agents in this clinical popula-

tion of youth. Existing studies in both adult and adolescent populations demonstrate that these medications can be taken safely with few adverse effects (Wilens et al. 1997). In one of the only studies to examine adverse effects in comorbid adolescent populations, Wilens et al. (1997) described four cases of male adolescents, aged 15–17 years, being treated with TCAs for ADHD who manifested transient cognitive changes, delirium, and tachycardia after smoking relatively low levels of marijuana. As with other psychotropic agents, clinicians should not confuse previously identified potential adverse effects associated with either the therapeutic agents or abusable substances with adverse events attributable to the concurrent use of therapeutic agents and abusive substances. Marijuana use can be associated with transient states of delirium, paranoia, nonspecific confusion, and psychosis (Thomas 1993); the majority of these reactions were at relatively higher doses of marijuana use. This observation raises the possibility that the concurrent use of a therapeutic agent and an abusable substance may make adverse effects more common and at a lower dose of either agent. Another possibility is the presence of an “adverse event or effect” resulting from the interaction of the substance and the individual’s psychopathology, for example, despite taking an anxiolytic, an anxious adolescent has panic attacks when using marijuana.

Our clinical experience is that most adolescents will respect a discussion of potential adverse effects and warnings about concomitant use of therapeutic agents and abusable substances. Unfortunately, rather than curtailing their substance use, many youth will purposefully be noncompliant in order to use substances and to avoid potential adverse effects or perceived risks of concomitant use.

THE PRACTICE OF PSYCHOPHARMACOLOGY IN ADOLESCENTS WITH SUBSTANCE USE DISORDERS

In considering pharmacotherapy for adolescents with comorbid SUD-psychiatric disorder, there are several important considerations including the medication’s proven potential effectiveness for similar populations, the medication’s potential for abuse or diversion, possible interactions with other medications or substances of abuse, and patient compliance (Fulton and Yates 1988; Kaminer 1995; FDA 1997; Horner and Scheibe 1997; Riggs 1998). Although optimal management may attempt to control psychiatric symptoms with short-term abstinence from substances of abuse and psychosocial therapies, persistence of the symptoms beyond several weeks should alert the clinician that antidepressants or other medications may be needed. Other factors that may prompt more aggressive medication treatment include (1) psychiatric symptoms clearly predating the substance use or abuse, (2) a significant family history of the psychiatric disorder, (3) past treatment failures and relapses, and (4) past successful treatment of the psychiatric disorder with medication.

The major objections to the use of psychoactive agents to treat substance

abusers has been the fear of abuse of that agent or seeming to promote a drug use philosophy that may prompt future use by adolescents. While understandable, there is no empirical evidence to support these fears. Emerging evidence suggests that for stimulants, adolescents who are treated with stimulants as adolescents have a lower risk for the development of SUDs than adolescents with ADHD who do not take stimulant medications (Biederman et al. 1999; Molina et al. 1999). Our clinical experience is that compliance with medication regimens is a bigger problem than abuse or diversion of medication treatments among adolescents.

Informed consent procedures should take care to explain both the potential benefits and interactions with substances of abuse and adverse effects of the recommended medications. The clinician should regularly ascertain compliance and ongoing level of substance use, utilizing toxicology to test the validity of the adolescent's report.

Although pharmacotherapy in adolescents with SUD should be well considered, based on a thorough evaluation and specific target symptoms, and combined with appropriate psychosocial interventions, the severity of dysfunction in these youth often dictates more aggressive treatment approaches, including pharmacotherapy.

SUMMARY

Pharmacological treatment approaches in adolescents with SUDs represent an important addition to the available treatment options for adolescents. The adult literature offers examples of many possible uses for pharmacological agents in the adolescent population. Unfortunately, the use of psychotropic medications for adolescents with SUD is severely limited by the paucity of empirically based research. Clearly, more psychopharmacological research utilizing adolescent SUD and comorbid populations is essential to advance our knowledge and clinical guidelines.

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20

Combination Pharmacotherapy

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Similar to the use of “add-on” or adjunctive pharmacotherapy in the treatment of congestive heart failure and epilepsy (Frye et al. 2000), medication combinations are being increasingly used for the treatment of child psychiatric disorders (Wilens et al. 1995). This emerging field of pediatric research (Findling et al. 1999, 2000) and clinical practice (Connor et al. 1998) may be partly driven by an apparent change in the treatment paradigm of psychopharmacological practice in the last few years, mainly an emphasis on the treatment of “target symptoms” (Pope and Hudson 1986), rather than specific diagnoses. In addition, high rates of child psychiatric comorbidity (Geller et al. 1996; Stephens and Sandor 1999) have motivated clinicians to consider treating pediatric patients with more than one single agent (Martin et al. 1999). In this chapter we briefly review the most common adult combination strategies and the child psychiatric disorders that may require combinations of pharmacotherapeutic agents.

BIPOLAR DISORDER

Controlled studies (Small et al. 1995) have shown that the combination of mood stabilizers often may be more efficacious than monotherapy for the acute (Frye et al. 2000) and maintenance (Denicoff et al. 1997) treatment of adult patients

with bipolar disorder (BPD). This trend is reflected in a reported increase in the average number of medications prescribed for a large sample of adult patients with BPD discharged from the National Institute of Mental Health (NIMH) (Clinical Center Research Unit of the Biological Psychiatry Branch) between 1974 and 1995 (Frye et al. 2000). Children with BPD may also be partially responsive to lithium monotherapy (Alessi et al. 1994), warranting a small number of pediatric combination pharmacotherapy studies conducted so far (Thase et al. 1989).

At the time of this publication, Findling and collaborators (2000) have completed the first phase of a controlled study examining the efficacy and safety of a combination of mood stabilizers in children and adolescents with BPD. This is an ongoing controlled study in which outpatients aged 5–17 years meeting diagnostic criteria for BPD Type I or II (and having experienced a manic or hypomanic episode within 3 months prior to baseline) are treated with both lithium and divalproex sodium (DVP) for up to 20 weeks in an open fashion and subsequently randomized to lithium or DVP maintenance monotherapy over an 8-week period (Thase et al. 1989). After enrolling 66 patients, preliminary results (not published) suggest that significant reductions in both manic and depressive symptoms compared to intake baseline are seen during the first 8 weeks of combination therapy (Thase et al. 1989). These preliminary results are promising and consistent with studies in adults showing that the combination of mood stabilizers may be more efficacious than monotherapy for maintenance therapy.

MAJOR DEPRESSIVE DISORDER

Traditional augmentation strategies of adult treatment-resistant depression have included the augmentation of selective serotonin-reuptake inhibitors (SSRIs) (Dinan 1993; Baumann et al. 1996), and monoamine oxidase inhibitors (MAOIs) (Himmelhoch et al. 1972; Price et al. 1985) with lithium. A variable response augmentation rate of SSRIs with lithium in adults with major depressive disorder (MDD) (Fara et al. 1994) has been replicated in two pediatric studies of augmentation of antidepressant therapy with lithium (Ryan et al. 1988; Strober et al. 1992).

Adult studies including bupropion (Marshall and Liebowitz 1996; Bodkin et al. 1997; Spier 1998), buspirone (Joffe and Schuller 1993; Bouwer and Stein 1997; Landen et al. 1998), desipramine (Zajecka et al. 1995), and mirtazapine augmentations of SSRIs (Carpenter et al. 1999) have not been replicated in pediatric populations.

LITHIUM AUGMENTATION

Ryan et al. in 1988 published a first report of lithium augmentation efficacy of tricyclic antidepressants (TCAs) in children. In this retrospective chart review,

14 adolescents with nonbipolar depression who did not respond adequately to a trial of TCAs and received subsequent augmentation with lithium were reviewed retrospectively by two research nurses not blind to treatment. The majority of the subjects had received at least 6 weeks of TCA treatment (and no further clinical improvement after week 8) before the addition of lithium for a period of at least 6 weeks. The mean age of this sample was 17 years old (Ryan et al. 1988). Five patients (36%) required hospitalization over the course of their illness. Six of 14 (43%) patients were considered responders (defined as patients improved to the point of being no more than mildly symptomatic or better) following the addition of lithium, 5 of 14 (36%) patients had little or no improvement after the addition of lithium, and 3 of 14 (21%) patients were considered partial responders (i.e., evidenced "some additional improvement") after lithium augmentation (Ryan et al. 1988). The severity of illness did not differ between the groups, nor did the mean serum lithium level for the responders (0.65 mEq/L) compared to the nonresponders (0.64 mEq/L). The group means severity rating at 4 weeks improved significantly at 6 weeks following the addition of lithium. Most responders experienced a gradual improvement in symptoms over the first month of lithium treatment. The most common side effects for patients on TCAs alone were anticholinergic side effects ($n = 12$) and dizziness ($n = 10$) and for the combination of lithium with TCAs were hand tremors ($n = 5$), dizziness ($n = 5$), nausea ($n = 5$), and dry mouth ($n = 5$) (Ryan et al. 1988). The conclusion drawn by the authors of this case report is that certain adolescents, previously unresponsive to TCAs, may respond to augmentation with lithium (Ryan et al. 1988). The duration of the prior TCA treatment was longer (i.e., 8 weeks) than the described length of TCA treatment in adults (i.e., 3 weeks), leading the authors to conclude that the therapeutic response was indeed a consequence of lithium augmentation rather than a time effect of the TCA treatment alone (Ryan et al. 1988). The data do not preclude that some patients might have improved with the passage of time alone, given the fluctuating course of the illness. This study merits controlled replication, especially considering the high switch rate of children with prepubertal MDD to prepubertal bipolarity (Geller et al. 1993).

Ryan et al.'s (1988) report was followed by an open trial of lithium augmentation in adolescent nonresponders to imipramine published by Strober et al. in 1992. In this 3-week open trial, 24 adolescents classified as nonresponders [i.e., less than 50% reduction on Hamilton Depression (HAM-D) scores and final score >10 after 6 weeks of treatment with imipramine] were compared with a case-control group of 10 adolescents nonresponders to imipramine who continued to receive imipramine monotherapy (Strober et al. 1992). Lithium was started at 900 mg in three divided doses and subsequently increased, depending on clinical response, to 0.7–1.2 mEq/L. The absolute magnitude of HAM-D change within each group was modest (i.e., average 14% reduction from baseline) (Strober et al. 1992), as was the nonsignificant difference between the two groups in average

HAM-D scores at the end of the trial. Nevertheless, the average HAM-D score for patients on lithium augmentation decreased from 18 points at the start of the trial to 13.4 points at the end of week 3, compared to a drop of 18.5 to 15.4 in the imipramine monotherapy group. The differential effect examined by computing the percentage of improvement in depression scores for each patient was significant between groups (i.e., average percentage of improvement of 26% for the lithium group compared to 16% for controls, $p < 0.05$, by *t*-test). Eight patients showed partial improvement during the 3-week trial, in contrast to one of the 10 controls. Lithium augmentation in this study was associated with few side effects, mainly polyuria and tremor ($n = 7$). The final estimates of 8% rate of clinically significant improvement and 33% rate of partial improvement, a much lower rate compared to adult studies of lithium augmentation (i.e., 65%) (Thase et al. 1989), suggests that lithium may have a potential use as an adjunctive strategy in some tricyclic-resistant adolescents with MDD, albeit less efficaciously than in adults with tricyclic-resistant MDD.

THYROID AUGMENTATION

Despite the documented efficacy of thyroid hormone augmentation of mood stabilizers and antidepressants (Bauer et al. 1998) in adults with affective disorders (Joffe et al. 1993), especially patients with rapid-cycling BPD (Bauer et al. 1998), no controlled studies of this potential treatment have been published in children and adolescents.

Two case reports (Weeston and Constantino 1996, Davanzo et al. 1999) have described the potential benefit of combining nimodipine, a dihydropyridine-type calcium antagonist, with thyroxine (T4) in high doses (175 µg/day) (Davanzo et al. 1999) and T4 with valproate (Weeston and Constantino 1996). In the first case report, a 13-year-old boy with refractory, ultradian rapid cycling BPD, achieved a 36-month sustained remission after nimodipine 180 mg daily was added to an ongoing treatment with 175 µg/day of thyroxine. No adverse effects were noticed. Medication response was partially attributed to adjunctive therapy with levothyroxine, although the authors noted that an attempt to taper thyroxine off was followed by recurrence of hypomania. In an earlier case report, a 13-year-old male adolescent with refractory rapid cycling BPD was stabilized for 9 months after levothyroxine (125 µg/day titrated over 10 days) was added to valproate 500 mg b.i.d. (Weeston and Constantino 1996). In this case report, the patient's pretreatment (baseline) free T4 level was 1.5 ng/dL, and his thyrotropin (TSH) level was 2.1 mIU/mL. After 6 weeks of thyroid augmentation treatment his free T4 level was 1.4 ng/dL, and his TSH level was less than 0.1 mIU/mL.

The potential risks and benefits of thyroid augmentation in bipolar children (Weeston and Constantino 1996) and adolescents have not been studied. Hospitalized adolescents with comorbid BPD and attention-deficit hyperactivity disorder

der (ADHD) reportedly have lower mean serum T4 concentration compared with patients with BPD alone (West et al. 1996). This and other observed differences in basal thyroid hormone levels in depressed and manic adolescents (Sokolov et al. 1994) may underlie important implications regarding the potential benefits of thyroid supplementation in adolescents with BPD and comorbid ADHD who do not respond to mood stabilizers alone (West et al. 1996).

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

The use of single agents in the treatment of ADHD may not be effective in 30–40% of children (Wilens and Biederman 1992). Although desipramine was prescribed in the past years for children with stimulant-resistant ADHD or in combination pharmacotherapy (Pataki et al. 1993; Rapport et al. 1993), cases of sudden-death onset on desipramine (Riddle et al. 1993) have diminished the enthusiasm for the prescription of desipramine in youngsters with ADHD or MDD.

Nortriptyline (NT) has instead seen resurgence as a second (or third)-line agent (Prince et al. 2000) for the treatment of comorbid or stimulant-refractory ADHD (Spencer et al. 1993). Its benefit in the treatment of ADHD was retrospectively evaluated by Wilens and colleagues (1993), who noted that 47% of a sample of 37 children and 21 adolescents with treatment-refractory, highly comorbid ADHD were receiving adjunctive medications in addition to NT. Nortriptyline treatment ranging from 0.4 to 4.5 mg/kg (average 2.0 mg/kg/daily) may have had an independent effect, since no association was found between response and concurrent pharmacotherapy. Mild adverse effects were reported in 20 subjects (34%) (Wilens et al. 1993).

TICS AND TOURETTE'S SYNDROME

It is well known that stimulants can exacerbate tics (Spencer et al. 1993). Conversely, it has been estimated that approximately 50% of patients with Tourette's syndrome (TS) may also meet the diagnostic criteria for ADHD (Spencer et al. 1993). Therefore, TCAs have been successfully used in children with this comorbidity. The therapeutic effectiveness of NT in the treatment of children with chronic tic disorder and ADHD was estimated from a chart review of 12 subjects with dual diagnosis (Spencer et al. 1993). Of the 12 patients treated with NT, 8 (67%) had significant improvement in tic symptomatology and 11 (92%) significantly improved ADHD symptoms over a follow-up period of 19 months, suggesting a therapeutic role for NT in the treatment of children with comorbid ADHD and tics (Spencer et al. 1993).

Likewise, aggressive behavior has been reported as a clinical problem in patients with TS (Stephens and Sandor 1999). No specific studies investigating

the effect of combination pharmacotherapy for the treatment of comorbid aggression in children with TS have been published to this date (Connor and Steingard 1996).

OBSESSIVE-COMPULSIVE DISORDER

Adult studies suggest that patients with obsessive-compulsive disorder (OCD) and concurrent chronic tic disorder refractory to treatment with SSRI monotherapy may preferentially respond to conjoint SSRI/neuroleptic therapy (McDougle et al. 1994). Analogously, in a retrospective chart review of 38 pediatric patients with OCD treated with fluoxetine, Geller and colleagues (Geller et al. 1995) reported that (successful) combination pharmacotherapy was required in 42% of the sample (Geller et al. 1995). The most commonly used pharmacotherapeutic combinations for the treatment of juvenile OCD—SSRI/benzodiazepines, SSRI/TCAs, and SSRI/mood stabilizers—have not been systematically evaluated in open or controlled pediatric studies (Geller et al. 1995).

PERVASIVE DEVELOPMENTAL DISORDER

The treatment of pervasive developmental disorder (PDD) requires appropriate behavioral and pharmacological interventions (Gilman and Tuchman 1995). Combination pharmacotherapy (i.e., two or more medications) was used in 16% of a sample of 109 children, adolescents, and adults (mean age = 13.9 years) diagnosed with higher functioning PDD (Martin et al. 1999). None of these pharmacological combinations has yet been systematically evaluated in open or controlled pediatric studies for the treatment of children and adolescents with PDD.

SUMMARY

The competent treatment of child psychiatric comorbid disorders requires a knowledge of the neurochemical correlates of each disorder and of the neurotransmitter interactions implicated in the use of combined pharmacological strategies. Controlled studies assessing the safety and efficacy of combined pharmacotherapy in child psychiatric disorders will assist in the development of guidelines and effective treatment strategies for children and adolescents presenting with psychiatric comorbidity.

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Index

- Abdominal pain, as side effect of psychostimulants, 142
- Abnormal cardiac physiology, 88–90
- Abnormal motor movements, as side effect of SSRIs, 266–267
- Absorption:
 - of antipsychotic agents, 358–359
 - of MAOIs, 318–319
 - of psychoactive drugs, 72–73
- Abuse (recreational abuse):
 - of clonidine or guanfacine, 566
 - of propranolol, 585
 - of psychostimulants, 145
- Academic achievement in children with ADHD, psychostimulants for, 124
- Acquired LOTS, 91
- Acquisition cost, definition/description of, 58
- Acute depression, lithium for, 423–424
- Acute dystonia, as side effect of antipsychotic agents, 375, 376
- Acute lithium intoxication, 437–438
- Acute mania, lithium for, 418–423
- Acute neuropsychiatric effects of SUDs, 686–688
 - alcohol, 686
 - anabolic steroids, 688
 - cannabis (marijuana), 686
 - cocaine and other stimulants, 686–687
 - hallucinogens, 687
 - inhalants, 687–688
 - opiates, 687
 - sedatives/hypnotics, 687
 - tobacco (nicotine), 688
- Acute violence, BZPs for, 516–517
- S-Adenosylmethionine (SAME), 619–620
- Adolescent depression:
 - MAOIs for, 328–329
 - prepubertal depression versus, 172

- Adrenergic agents, 543–595, 635
 beta-blockers, 574–588
 abuse of, 585
 available preparations and cost, 585, 586
 chemical properties, 576–577
 clinical practice: dosage and administration, 588
 contraindications, 581–582
 drug interactions, 585, 586
 clonidine and guanfacine, 543–573
 available preparations and cost, 566, 567
 clinical practice, 568–570
 chemical properties, 544–545
 contraindications, 558–560
 dosage and administration—transdermal therapeutic system, 570–571
 drug interactions, 566, 567
 important considerations when prescribing, 565–566
 indications for, 545–558
 initiating and maintaining treatment, 566–568
 oral clonidine, management of specific side effects, 570–571
 side effects, 560–565
 skin patch, management of specific side effects, 572–573
 withdrawal from, 573–574
 Adult patterns of ATD treatment, late adolescent ATD treatment versus, 38
 Adverse reactions to antipsychotic agent, 373–381
 Age-specific patterns of α -agonists, 39
 Age-specific prevalence of stimulant medication for ADHD, 27
 Aggression:
 in adolescents with SUDs, 699–700
 anticonvulsants for, 457–458
 in brain-damaged children and adolescents, propranolol for, 577–578
 BZPs for, 516–519
 clonidine or guanfacine for, 554–555
 [Aggression]
 lithium for, 428–429
 as side effect of CBZ, 462
 α -Agonists, 24, 38–39
 Agoraphobia, MAOIs for, 330–331
 Agranulocytosis:
 as side effect of antipsychotic agents, 381
 as side effect of CBZ, 463
 AIDS, adverse psychoactive drug reactions to, 664–665
 Akathisia:
 clonidine or guanfacine for, 558
 propranolol for, 579–580
 as side effect of antipsychotic agents, 375–376
 as side effect of SSRIs, 266–267
 Alcohol:
 acute neuropsychiatric effects of, 686
 chronic neuropsychiatric effects of, 688
 Allergies (allergic reactions):
 clonidine or guanfacine contraindicated for, 560
 lithium contraindicated for, 432
 propranolol contraindicated for, 582
 as side effect of SSRIs, 260, 270
 TCAs contraindicated for, 196
 Alopecia, as side effect of DVP, 466
 Alprazolam, 510
 Amitriptyline:
 available preparations and cost of, 208
 dosage and regime for ADHD, 182
 dosage and regime for enuresis, 184
 dosage and regime for MDD, 180
 FDA advertising guidelines for, 208
 neurotransmitter effects of, 170
 Amphetamines, 2
 molecular structure of, 116
 Amyl nitrite, 1
 Anabolic steroids, acute neuropsychiatric effects of, 688
 Analytic perspective, definition/description of, 58

- Anorexia nervosa:
MAOIs for, 333
as side effect of psychostimulants, 142
SRRIs for, 256–257
TCAs for, 192
- Antianxiety agents, effects on cardiovascular system of, 98
- Anticholinergic agents, 1
effects of:
antipsychotic agents, 374, 376
clonidine and guanfacine, 564
SSRIs, 271
TCAs, 202
- Anticipatory anxiety associated with medical procedures, BZP for, 507–508
- Anticonvulsants, 453–488, 635
available preparations and cost, 474
chemical properties, 454
contraindications, 459–460
drug interactions, 471–473
indications for, 454–459
initiating and maintaining treatment, 473–477
new (third-generation) anticonvulsants, 477–479
pharmacokinetics, 469–471
side effects, 460–469, 470
- Antidepressants (ATD), 3, 4, 24, 35–38
in concomitant psychotropic medication, 40–41
effects on cardiovascular system of, 98
See also Novel (typical) antidepressants; Tricyclic antidepressants (TCAs)
- Antihistamines, 497–499
absorption and metabolism of, 497–499
available preparations and costs of, 498
contraindications, 520
drug interactions with, 526
initiating and maintaining treatment, 528
- [Antihistamines]
for insomnia, 513–514
management of specific side effects, 529
mechanism of action, 499
overdose of, 523
risks for abuse/dependence, 525
side effects, 522–523
withdrawal from, 529–530
- Antipsychotic agents, 355–414, 635
atypical agents, 387–402
clozapine, 387–391
olanzapine, 393–395
quetiapine, 391–393
risperidone, 395–400
ziprasidone, 400–402
conventional (typical) agents, 356–387
absorption and metabolism, 358–359
abuse/dependence, 382
available preparations, 382
chemical properties, 356–358
contraindications, 371–373
indications for, 359–369
initiating and maintaining treatment, 383–386
nonspecific behavioral problems, 369–370
overdose, 381
side effects and adverse reactions, 373–381
use in pediatric medicine, 370–371
withdrawal from typical agents, 386–387
effects on cardiovascular system of, 100–101
- Anxiety (anxiety disorders), 71
ADHD in children with, psychostimulants for, 131
anxiolytic drugs for, 500–508
anticipatory anxiety associated with medical procedures, 507–508
generalized anxiety disorders, 503–505

- [Anxiety (anxiety disorders)]
 obsessive-compulsive disorder, 506–507
 panic disorder, 500–502
 posttraumatic stress disorder, 505–506
 separation-anxiety disorder/school refusal, 502–503
 social anxiety disorder, 507
 clonidine or guanfacine for, 557, 565
 MAOIs for, 330–332
 SSRIs for, 252–254
 TCAs for, 185–187, 204
See also Generalized anxiety disorders
- Anxiolytics, 489–541
 abuse/dependence, 523–525
 adverse effects, 520–523
 available preparations and cost, 493, 498, 525
 chemical properties, 490–499
 contraindications, 520
 dosing guidelines for use with children and adolescents, 527
 drug interactions, 525, 526
 indications for, 499–520
 initiating and maintaining treatment, 525–528
 management of specific side effects, 528–529
 overdose, 523
 withdrawal from, 529–530
- Aplastic anemia, as side effect of CBZ, 463
- Appetite increase (or decrease):
 as side effect of clonidine and guanfacine, 564–565
 as side effect of DVP, 467
- Atenolol:
 available preparations and cost of, 585, 586
 pharmacokinetics of, 546, 576
- Atrial fibrillation, 89
- Attention-deficit disorder without hyperactivity, TCAs for, 194
- Attention-deficit hyperactivity disorder (ADHD), 3–4, 23–24, 52, 71
 in adolescents with SUDs, 696–699
 anticonvulsants for, 459
 antipsychotic agents for, 369
 BZPs for, 518–519
 in children and adolescents, psychostimulants for, 119–135, 152
 with anxiety disorders, 131
 with conduct disturbances, 131
 with developmental disabilities, 131–132
 with fragile X syndrome, 132
 with head trauma and/or organic brain disease, 132–133
 with mental retardation, 132
 with tic disorders, 133–134
 clinical factors and special need populations influencing drug prevalence, 29–30
 clonidine or guanfacine for, 551–554
 clinician's guide to using clonidine, 568
 clinician's guide to using guanfacine, 573
 combination pharmacotherapy for, 715
 dietary intervention in children with, 603
 dosage and regimen of TCAs for, 182
 estimates of ADHD youths receiving stimulant treatment, 25–26
 high-dose vitamin therapy for, 603–604
 international perspectives on, 34–35
 lithium for, 429
 MAOIs for, 331
 medication issues related to drug utilization, 31–32
 methylphenidate as drug of choice in treatment of, 149–153
 other factors influencing prevalence of treatment for, 33–35
 patient demographic factors for, 27–29
 in preschool children, 129–130

- [Attention-deficit hyperactivity disorder (ADHD)]
- prevalence of stimulant medication treatments for youths, 26–27
 - prevalence of stimulant treatment according to educational setting and category, 32–33
 - psychostimulants provided for, 113–116
 - SSRIs for, 251–252
 - stepwise progression to the pharmacological treatment of, 127
 - stimulant medication for ADHD youths in foster care, 31
 - stimulant medication for mentally retarded students with, 30
 - TCAAs for, 178–183
 - thyroid hormone therapy for, 608
 - trazadone for, 301–302
 - treatment and medication visit rates, 26
 - types of medication prescribed for, 24
- Atypical and adjunctive agents, 597–633
- herbal medication and dietary supplements, 609–622
 - nutritional therapy, 602–606
 - opiate antagonists, 597–602
 - secretin and autism, 606–607
 - thyroid hormone treatment, 607–609
- Atypical antidepressants. *See* Novel (atypical) antidepressants
- Atypical antipsychotic agents, 387–402
- clozapine, 387–391
 - olanzapine, 393–395
 - quetiapine, 391–393
 - risperidone, 395–400
 - ziprasidone, 400–402
- Atypical depression, MAOIs for, 324–326
- Autism:
- clonidine or guanfacine for, 555
 - high-dose vitamin therapy for, 605
 - opiate antagonists for, 600–601
 - secretin and, 606–607
 - TCAAs for, 192–193
 - thyroid hormone therapy for, 608
- Average cost, definition/description of, 58
- Aversive therapy, as SUDs treatment, 694–695
- Barbiturates, 2
- Behavioral disorders:
- antipsychotic agents for, 386
 - as side effect of SSRIs, 268–270
- Benzodiazepines (BZPs), 490–494, 635
- absorption and metabolism of, 490–492
 - approved indications for, 510
 - available preparations and costs of, 493, 525
 - chemical structure of, 491
 - contraindications, 520
 - drug interactions with, 526
 - effects on cardiovascular system of, 98
 - initiating and maintaining treatment, 525–526
 - mechanism of action, 492–494
 - for nonspecific childhood anxiety symptoms, 504
 - overdose of, 523
 - risks for abuse/dependence, 523–524
 - side effects of, 520–522
 - managing specific side effects, 528–529
 - withdrawal from, 529
- Beta-blockers, 574–588
- abuse of, 585
 - available preparations and cost, 585, 586
 - chemical properties, 576–577
 - clinical practice: dosage and administration, 588
 - contraindications, 581–582
 - drug interactions, 585, 586
 - indications for, 578–581
 - initiating and maintaining treatment, 585–588
 - pharmacokinetics, 576
 - side effects, 582–585
 - in treatment of LQTS, 91

- Bioavailability of psychoactive drugs, 72–73
- Bioethics:
 research in, 19–20
 resources on the Web, 11
 step-wide approach to examination of, 18–19
- Biological abnormalities in child and adolescent depression, 174–175
- Bipolar affective disorder:
 in adults, clonidine or guanfacine for, 556
 thyroid hormone therapy for, 608
- Bipolar depression, MAOIs for, 327–328
- Bipolar disorder (BPD):
 in adolescents with SUDs, 696
 anticonvulsants for, 455–457
 combination pharmacotherapy for, 711–712
 lithium for, 424
 acute depression, 423–424
 acute mania, 418–423
- Blood dyscrasias, as side effect of CBZ, 463–464
- Blood glucose, increase in, as side effect of clonidine and guanfacine, 565
- Blood pressure:
 as guideline for use of TCAs in children and adolescents, 203
 psychostimulants contraindicated for, 138–139
- Borderline personality disorder (BPD):
 clonidine or guanfacine for, 558
 MAOIs for, 334–335
 SSRIs for, 259
 TCAs for, 193
- Brain development, impact of SSRIs on, 271–272
- Bronchoconstriction, as side effect of propranolol, 584
- Bronchospastic disease, propranolol contraindicated for, 581
- Bulimia nervosa:
 lithium for, 430
 MAOIs for, 333–334
 SSRIs for, 257–258
 TCAs for, 191–192
- Bupropion, 24, 300–305, 712
 chemical properties, 301
 cognitive effects, 303
 contraindications, 302
 dosage and administration, 306
 drug interactions with, 304–305
 FDA advertising guidelines for, 208
 indications for, 301–302
 neurotransmitter effects of, 170
 seizure disorder-related precautions, 302–303
 other side effects, 303
- Buspirone, 496–497, 712
 absorption and metabolism, 495
 chemical structure, 496
 contraindications, 520
 drug interactions with, 526
 initiating and maintaining treatment, 526–528
 for insomnia, 513
 mechanism of action, 495–497
 overdose of, 523
 risks for abuse/dependence, 524–525
 side effects, 522
 managing specific side effects, 529
 withdrawal from, 529–530
- Cachexia, adverse psychoactive drug reactions to, 665–666
- Calcium channel blockers, effects on cardiovascular system of, 103
- Cannabis (marijuana), 1
 acute neuropsychiatric effects of, 686
 chronic neuropsychiatric effects of, 688
- Carbamazepine (CBZ), 453
 available preparations and cost of, 474
 chemical properties, 454
 contraindications, 459–460
 drug interactions with, 472
 effects on cardiovascular system of, 102
 indications for, 454–459
 initiating and maintaining treatment, 475–476
 overdose/toxicity, 469
 side effects of, 460–465

- Cardiac problems:
arrhythmias, 88–89
psychostimulants contraindicated for cardiac/blood pressure anomalies, 138–139
as side effect of lithium, 435
See also Psychotropic medication, cardiac side effects of
- Cardiovascular disorders:
clonidine or guanfacine contraindicated for, 559
lithium contraindicated for, 432
MAOIs and, 341, 345
propranolol contraindicated for, 582
psychoactive drug interactions in, 648–649
as side effect of clonidine and guanfacine, 562–563
as side effect of TCAs, 197–198
SSRIs and, 271
- Catapress transdermal (skin patch), available preparations and cost of, 566, 567
- Chemical hepatitis, as side effect of psychostimulants, 144
- Childhood depression, MAOIs for, 328–329
- Chlorazepate, 510
- Chlordiazepoxide, 510
major metabolic pathways of, 492
- Chlorpromazine, 2
available preparations and average cost of, 384
clinical potency, 357
nonpsychiatric pediatric indications for, 361
potency for common side effects, 358
psychiatric indications and approved age ranges for, 360
- Chlorprothixene:
available preparations and average cost of, 385
clinical potency, 357
psychiatric indications and approved age ranges for, 360
- Chronic aggression, BZPs for, 517–518
- Chronic hair pulling, lithium for, 430
- Chronic neuropsychiatric effects of substance abuse, 688–690
- Chronic pain syndrome, TCAs for, 194–195
- Citalopram, 224
available preparations and cost of, 275
clinical profile, 225
dosage and administration, 279
half-life and metabolic pathways, in OCD treatment, 247
indicators for, in child and adolescent psychiatry, 231
molecular structure of, 227
pharmacokinetics of, in children and adolescents, 229
- Clinical pharmacology of psychoactive drugs, 71–85
absorption and bioavailability, 72–73
distribution, 73
dosing considerations in children, 80–82
effect of development and drug disposition on children, 79–80
elimination, 78–79
metabolism, 73–78
- Clomipramine:
dosage and regime for ADHD, 182
dosage and regime for enuresis, 184
dosage and regime for MDD, 180
dosage and regime for OCD, 190
half-life and metabolic pathways, in OCD treatment, 247
intravenous, for major depressive disorders, 177
- Clonidine and guanfacine, 4, 38–39, 543–574
available preparations and cost of, 566, 567
in concomitant psychotropic medication, 40–41
diagnosis and treatment combinations associated with, 39
dosage and administration of oral clonidine, 568–570
effects on cardiovascular system of, 102–103
indications for, 547

- [Clonidine and guanfacine]
 - management of specific side effects
 - of oral clonidine, 570–571
 - molecular structure of, 544
 - pharmacokinetics of, 546
 - withdrawal from, 573–574
- Clonidine skin patch, 566, 567
 - dosage and administration of, 571–572
 - management of specific side effects of, 572–573
- Clorgyline, chemical structure of, 319
- Clozapine, 387–391
 - available preparations and average cost of, 385
 - clinical potency, 357
 - potency for common side effects, 358
- Cocaine:
 - acute neuropsychiatric effects of, 686–687
 - chronic neuropsychiatric effects of, 688
- Cognitive ability, decrease in, as side effect of psychostimulants, 143
- Combination pharmacotherapy, 711–719
 - ADHD, 715
 - bipolar disorder, 711–712
 - lithium augmentation, 712–714
 - major depressive disorder, 712
 - obsessive-compulsive disorder, 716
 - pervasive developmental disorder, 716
 - thyroid augmentation, 714–715
 - tics and Tourette's syndrome, 715–716
- Comorbidity of physical and psychiatric disorders, 636–639
 - drug/disease interaction, 645–660
 - cardiovascular disease, 648–649
 - diabetes mellitus, 652–653
 - gastrointestinal disease, 647–648
 - hematological disorders, 653
- [Comorbidity of physical and psychiatric disorders]
 - hepatic disease, 646–647
 - neurological disorders and epilepsy, 651–652
 - pulmonary disease, 649–651
 - renal disease, 647
- Comparison groups in child psychopharmacology clinical trials, ethical issues related to choice of, 11–13
- Concomitant psychotropic medication
 - treatment of youths, 40–41
- Conduct disorder:
 - anticonvulsants for, 457–458
 - in children with ADHD, psychostimulants for, 131
 - lithium for, 428–429
 - TCAs for, 193–194
- Confusion, as side effect of TCAs, 204
- Congenital heart disease, 90
- Congenital long QT syndrome, 90–92
- Congenital malformations, as side effect of CBZ, 462
- Congestive heart failure, as side effect of propranolol, 583
- Consent/assent forms, 15–16
- Contact stomatitis, as side effect of lithium, 434
- Contingent valuation, definition/description of, 58
- Cost/QALY, definition/description of, 58
- Cost-benefit analysis (CBA), 56
 - definition/description of, 58
- Cost-benefit ratio, definition/description of, 58
- Cost-effective analysis (CEA), 53–54, 57
 - definition/description of, 58
 - importance of use in childhood and adolescent mental disorders and treatment, 65–66
 - reporting checklist, 64
 - two forms of, 57

- Cost-effectiveness ratio, definition/description of, 58
- Cost-minimization analysis, definition/description of, 58
- Cost (burden)-of-illness, definition/description of, 58
- Cost of mental disorders, 65–66
- Costs, measuring costs in health economics, 60–62
- Cost-utility analysis (CUA), 57
 - definition/description of, 58
- Craving, deduction and blocking strategies for, 693–694
- Critical concerns in children with ADHD, psychostimulants for, 125
- Cyclosporine, 72
- Cyclothymia, lithium for, 424–425
- CYP3A4 enzymes, 72, 74
- Cytochrome P450 (CYP) enzymes, 72, 74, 655,
 - characteristics of, 75
 - ontogeny of, 79–80
 - potential substrates, inducers, and inhibitors for, 656–660
- Data and safety monitoring boards (DSMB), 17
- Decision analysis, definition/description of, 58
- Decision tree:
 - definition/description of, 58
 - about pediatric research, 10
- Decreased cognitive ability, as side effect of psychostimulants, 143
- Dehydration, lithium contraindicated for, 432
- Delirium, adverse psychoactive drug reactions to, 660–663
- Depressed heart rate, as side effect of propranolol, 582–583
- Depression, 52–53, 71, 171–176
 - abnormal DST, 175
 - in adolescents with SUDs, 695–696
 - biological abnormalities in, 174–175
 - BZPs for, 519
 - [Depression]
 - clonidine contraindicated for, 558–559
 - electroencephalography and, 175
 - endogenous and anxious factors in, 172
 - family history of, 173–174
 - indications for pharmacotherapy, 176
 - lithium for, 423–424, 425–426
 - MAOIs for, 323–329
 - neuroimaging, 175–176
 - in prepubertal children and adolescents, 4–5
 - propranolol contraindicated for, 582, 584
 - as side effect of clonidine and guanfacine, 563
 - symptom frequency and severity, 171–172
 - unipolar
 - thyroid hormone therapy for, 607–608
 - lithium for, 425–426
 - See also* Major depressive disorders (MDDs)
- Dermatological problems, as side effect of lithium, 434
- Desipramine, 24, 88
 - available preparations and cost of, 208
 - dosage and regime for ADHD, 182
 - dosage and regime for enuresis, 184
 - dosage and regime for MDD, 180
 - FDA advertising guidelines for, 208
 - neurotransmitter effects of, 170
- Developmental disabilities in children with ADHD, psychostimulants for, 131–132
- Dexamethasone suppression test (DST), 175
- Dextroamphetamine, 23, 24, 113
 - available preparations and cost of, 149
 - biphasic action of, 120, 121
 - dosage ranges, 152
 - drug interactions with, 148

- [Dextroamphetamine]
 - pharmacokinetics in children and adolescents, 115, 117
 - psychostimulant properties of, 158
- Dextroamphetamine/adderall, 153–156
- Diabetes:
 - development of, as side effect of lithium, 436
 - propranolol contraindicated for, 581
 - psychoactive drugs interactions in, 652–653
 - TCAs contraindicated for, 196
- Diazepam, 510
 - major metabolic pathways of, 492
- Dietary restrictions necessary for MAOI therapy, 338–339
- Dietary supplements. *See* Herbal medications and dietary supplements
- Dipolia, as side effect of CBZ, 461
- Direct medical costs, definition/description of, 58
- Direct nonmedical cost, definition/description of, 59
- Discount rate, definition/description of, 59
- Disrupted sleep, as side effect of clonidine and guanfacine, 564
- Distractibility in children with ADHD, psychostimulants for, 123
- Distribution of psychoactive drugs in the body, 73
- Divalproex sodium (DVP), 24, 453, 712
 - available preparations and cost of, 474
 - chemical properties, 454
 - contraindications, 459–460
 - indications for, 455–459
 - initiating and maintaining treatment, 476–477
 - overdose/toxicity, 469
 - side effects of, 465–469
- Dizziness:
 - as side effect of clonidine and guanfacine, 563
 - as side effect of propranolol, 585
- Dosing considerations for psychoactive drugs, 80–81
- Down syndrome, thyroid hormone therapy for, 608–609
- Doxepin:
 - dosage and regime for ADHD, 182
 - dosage and regime for enuresis, 184
 - dosage and regime for MDD, 180
- Dreaming, as side effect of SSRIs, 266
- Droperidol:
 - available preparations and average cost of, 385
 - clinical potency, 357
- Drug abuse:
 - as side effect of psychostimulants, 145
 - SSRIs for, 256
 - See also* Substance abuse disorders (SUDs)
- Drug interactions:
 - with anticonvulsants, 471–473
 - with bupropion, 304–305
 - with clonidine or guanfacine, 566, 567
 - with lithium, 438, 439
 - with propranolol, 585
 - with psychostimulants, 147–148
 - with SSRIs, 273, 274
 - with TCAs, 206–207
 - with trazadone, 300
- Dry mouth, as side effect of SSRIs, 267
- Dysphoria, as side effect of psychostimulants, 142
- Dysthymia, TCAs for, 194
- Eating disorders:
 - MAOIs for, 333–334
 - opiate antagonists for, 601
 - See also* Anorexia nervosa; Bulimia nervosa
- ECG, as guideline for use of TCAs in children and adolescents, 203

- Economic status, stimulant medication for ADHD and, 28, 29
- Edema, as side effect of lithium, 435
- Education:
 importance in psychopharmacological management of the physically ill child, 642–643
 stimulant treatment for ADHD and educational setting and category, 32–33
- EEG worsening, as side effect of CBZ, 461
- Effectiveness (of a drug), definition/description of, 59
- Electroconvulsive therapy (ECT):
 lithium contraindicated for, 432
 for major depressive disorders, 177–178
- Elimination, psychoactive drugs and, 78–79
- Emotion in children with ADHD, psychostimulants for, 125
- Enuresis, TCAs for, 183–185, 367
- Epilepsy:
 psychoactive drug interactions in, 651–652
 TCAs contraindicated for, 196
- Estazolam, 510
- Ethical issues in pediatric psychopharmacology research, 7–22
 consent/assent forms, 15–16
 data and safety monitoring boards, 17
 general principles, 8–10
 reimbursements to study participants, 17
 research in bioethics, 19–20
 step-wise approach to examining bioethics, 18–19
 transition of research participants to individualized clinical care, 17–18
 treatment studies, 11–15
- Ethnicity/race:
 α -agonist patterns and, 39
 ATD medication patterns and, 37
 stimulant prevalence for ADHD and, 28
- Exogenous obesity, psychostimulants for, 129
- Extrapyramidal symptoms (EPS), as side effect of antipsychotic agents, 374–375, 376
- Familial history, TCA side effects and, 198
- Fatigue:
 adverse psychoactive drug reactions to, 665–666
 as side effect of lithium, 435
- FDA:
 advertising guideline for TCAs, 208
 approval and indications for MAOIs, 320
- Fibrillation, 89
- Fluid retention, as side effect of clonidine and guanfacine, 565
- Fluoxetine, 71, 77, 224
 available preparations and cost of, 275
 clinical profile, 225
 dosage and administration of, 278
 FDA advertising guidelines for, 208
 half-life and metabolic pathways, in OCD treatment, 247
 indicators for, 231
 molecular structure of, 226
 neurotransmitter effects of, 170
 pharmacokinetics, 229
- Fluphenazine:
 available preparations and average cost of, 384
 clinical potency, 357
 potency for common side effects, 358
- Flurazepam, 510
 major metabolic pathways of, 492
- Fluvoxamine, 77, 224
 available preparations and cost of, 275
 clinical profile, 225
 dosage and administration of, 278
 half-life and metabolic pathways, in OCD treatment, 247
 indicators for, 231
 molecular structure, 228
 pharmacokinetics, 229

- Formulary, definition/description of, 59
- Foster care, stimulant medication for
ADHD youths in, 31
- Fragile X syndrome:
ADHD in children with, psychostimulants for, 132
clonidine or guanfacine for, 555–556
high-dose vitamin therapy for, 604–605
- Gabapentin, 453, 477–479
- Gastrointestinal problems:
psychoactive drug interactions in, 647–648
as side effect of DVP, 466–467
as side effect of lithium, 433
as side effect of SSRIs, 262–264
- Gender-specific prevalence:
for α -agonists, 39
for ATD medication patterns, 37
for treatment of ADHD, 28
- Generalized anxiety disorder:
BZP for, 503–505
propranolol for, 579
- Geographic region, stimulant medication for ADHD and, 29
- Ginkgo (*Ginkgo biloba*), 613–614
- Ginseng (*Panax spp.*), 616–617
- P-Glycoprotein, 72
- Growth hormone (GH) regulation, impact of propranolol on, 584
- Growth retardation:
psychostimulants contraindicated for, 137–138, 143
as side effect of lithium, 436
- Group A betahemolytic streptococcal (GABHS) infections, 248–250
- Guanfacine, 38–39
available preparations and cost of, 566, 567
indications for, 547
molecular structure, 544
pharmacokinetics, 546
withdrawal from, 573–574
See also Clonidine and guanfacine
- Hair loss, as side effect of SSRIs, 270–271
- Hallucinations, as side effect of propranolol, 584
- Hallucinogens, acute neuropsychiatric effects of, 687
- Haloperidol, 77
available preparations and average cost of, 385
clinical potency, 357
psychiatric indications and approved age ranges for, 360
- Headache:
adverse psychoactive drug reactions to, 667–668
as side effect of clonidine and guanfacine, 563
- Head trauma in children with ADHD, psychostimulants for, 132–133
- Health economic evaluations. *See* Pharmacoeconomics research
- Heart period variability, 94–95
- Heart rate, 94–95
- Hematological disorders:
psychoactive drug interactions in, 653
as side effect of CBZ, 463
- Hepatic disease, psychoactive drug interactions in, 646–647
- Herbal medications and dietary supplements, 609–622
gingko, 613–614
ginseng, 616–617
inositol, 620–621
kava kava, 614–615
melatonin, 617–619
omega-3 fatty acids, 621–622
S-adenosylmethionine (SAME), 619–620
St. Johns wort, 610–613
valerian, 615–616
- High cholesterol levels, as side effect of CBZ, 463
- High-dose vitamin therapy, 603–606
- Historical perspective, 1–6
- HIV/AIDS, adverse psychoactive drug reactions to, 664–665

- Human capital method:
 approach to health economics, 61
 definition/description of, 59
- Hyperactivity:
 in children with ADHD, psychostimulants for, 123
 in children with PDD, opiate antagonists for, 599–600
 as side effect of psychostimulants, 143
 as side effect of SSRIs, 268–270
- Hyperprolactinemia, adverse reactions to antipsychotic agents and, 376, 381
- Hypertension:
 rebound in, as side effect of clonidine and guanfacine, 563–564
 as side effect of MAOIs, 344–345
 as side effect of psychostimulants, 143–144
 as side effect of TCAs, 202
- Hyperthyroidism, propranolol contraindicated for, 582
- Hypnotics/sedatives:
 acute neuropsychiatric effects of, 687
 chronic neuropsychiatric effects of, 688
- Hypoglycemia, propranolol and, 581, 584
- Hypomania, as side effect of SSRIs, 268–270
- Hyponatremia, as side effect of CBZ, 464
- Hypotension:
 orthostatic, 93–94
 side effects of trazadone on, 299–300
 as side effect of clonidine and guanfacine, 562
 as side effect of propranolol, 585
- Hypothyroidism, as side effect of lithium, 434
- Hysteroid dysphoria, MAOIs for, 335
- Idiopathic ventricular tachycardia (IVT) in normal hearts, 92
- Imipramine:
 available preparations and cost of, 208
 dosage and regime for ADHD, 182
 dosage and regime for enuresis, 184
 dosage and regime for MDD, 180
 FDA advertising guidelines for, 208
 neurotransmitter effects of, 170
- Impulsivity, as side effect of CBZ, 462
- Incoordination, as side effect of TCAs, 204
- Incremental cost, definition/description of, 59
- Incremental cost-effectiveness, 57
- Indirect cost, definition/description of, 59
- Inhalants, acute neuropsychiatric effects of, 687
- Inositol, 620–621
- Insomnia, 508–514
 BZP for, 509–513
 mirtazapine for, 308
 non-BZP sleep agents and, 513
 as side effect of psychostimulants, 140–141
 as side effect of SSRIs, 265
 as side effect of TCAs, 204
- Intangible cost, definition/description of, 59
- Interactions of metabolic drugs, 77–78
- Intermittent explosive disorder (IED), anticonvulsants for, 458–459
- Iopiramate, 453
- Irritability:
 as side effect of CBZ, 462
 as side effect of clonidine and guanfacine, 563
 as side effect of psychostimulants, 142
- Isocarboxazid, chemical structure of, 319
- Kava kava (*Piper methysticum*), 614–615
- Lamotrigine, 453, 477–479
- Leukocytosis, as side effect of lithium, 435

- Leukopenia, as side effect of CBZ, 463
- Lithium, 415–452, 635, 712
 abuse, 438
 available preparations, 438–439
 chemical properties, 416
 contraindications, 431–432
 dosage and administration, 442–445
 drug interactions with, 437, 439
 effects on cardiovascular system of, 100–101
 indications for, 418–431
 initiating and maintaining treatment, 439–441
 mechanisms of action, 416–418
 as part of combination therapy, 712–714
 propranolol for lithium tremor, 580
 side effects, 432–438
 treatment for youths with diagnosis of ADHD, 25–26
- Liver disease:
 clonidine or guanfacine contraindicated for, 560
 SSRIs contraindicated for, 262
- Liver functioning, impaired:
 psychostimulants contraindicated for, 139–140
 as side effect of psychostimulants, 144
- Liver toxicity:
 as side effect of CBZ, 464
 as side effect of DVP, 467–468
- Long QT syndrome (LQTS), 90–92
 acquired, 91
 management of, 91–92
- Lorazepam, 510
- Loxapine:
 available preparations and average cost of, 385
 clinical potency, 357
- Magnesium pemoline. *See* Pemoline
- Major depressive disorders (MDD), 176–178, 180
 anticonvulsants for, 457
 [Major depressive disorders (MDD)]
 combination pharmacotherapy for, 711–712
 current practices, 178, 180
 dosages and regimes of TCAs for, 180
 electroconvulsive therapy for, 177–178
 intravenous clomipramine for, 177
 mirtazapine for, 307–308
 SSRIs for, 230–233
 trazadone for, 302
- Malaise, as side effect of lithium, 435
- Male reproductive system:
 effect of CBZ on, 464–465
 effect of SSRIs on male sexual dysfunction, 267
- Mania:
 as side effect of MAOIs, 341
 as side effect of TCAs, 202
- MAOIs. *See* Monoamine oxidase inhibitors (MAOIs)
- Maprotilene:
 available preparations and cost of, 208
 dosage and regime for ADHD, 182
 dosage and regime for enuresis, 184
 dosage and regime for MDD, 180
 effects on cardiovascular system of, 100
 FDA advertising guidelines for, 208
 neurotransmitter effects of, 170
- Marginal cost-effectiveness, 57
- Marginal costs, definition/description of, 59
- Marijuana. *See* Cannabis (marijuana)
- Medications contraindicated with MAOIs, 337
- Melatonin, 617–619
- Menstrual disorders:
 adverse psychoactive drug reactions to, 669–670
 as side effect of DVP, 468
- Mental retardation:
 in children with ADHD, psychostimulants for, 132

- [Mental retardation]
 - high-dose vitamin therapy for, 605–606
 - stimulant medication for ADHD and, 30
- Mesoridazine:
 - available preparations and average cost of, 384
 - clinical potency, 357
- Metabolism:
 - of antipsychotic agents, 358–359
 - of MAOIs, 318–319
 - of psychoactive drugs, 73–78
- Methodology for Epidemiology of Mental Disorders in Children and Adolescents (MECA), 52
- Methylphenidate (Ritalin), 3, 4, 23, 24, 71, 113–114
 - available preparations and cost of, 149
 - in concomitant psychotropic medication, 40–41
 - dosage ranges, 152
 - drug interactions with, 147
 - as drug of choice in treatment of ADHD, 149–153
 - molecular structure, 116
 - pharmacokinetics in children and adolescents, 115, 117
 - psychostimulant properties, 158
- Metoclopramide, nonpsychiatric pediatric indications for, 361
- Metoprolol, pharmacokinetics of, 576
- Mianserin, effects on cardiovascular system of, 100
- Midazolam, 510
- Migraine. *See* Headache
- Mirtazapine, 307–309
 - dosage and administration, 308
 - indications for, 307–308
 - side effects, 308–309
- Mitral valve prolapse (MVP), 92–93
- Moclobemide, 77, 322–323
 - chemical structure, 319
- Molindone:
 - available preparations and average cost of, 385
 - clinical potency, 357
- Monoamine oxidase inhibitors (MAOIs), 2, 93–94, 317–354, 712
 - abuse/dependence, 342
 - available preparations and cost of, 342–343
 - chemical properties, 318–322
 - contraindications, 335–336, 337, 338–339
 - dosage and administration, 343–344
 - drug interactions with, 342
 - effect on cardiovascular system of, 100
 - indications for, 323–335
 - initiating and maintaining treatment, 343
 - moclobemide, 322–323
 - overdose, 342
 - propranolol contraindicated for, 582
 - psychostimulants contraindicated for patients on, 140
 - side effects, 336–341
 - management of specific side effects, 344–345
 - SSRIs contraindicated for patients on, 260
 - TCAs contraindicated for, 196
 - withdrawal from, 345–346
- Mood disorders (mood swings):
 - in adolescents with SUDs, 695–696
 - in children with ADHD, psychostimulants for, 125
- Mood stabilizers:
 - effects on cardiovascular system of, 101–102
 - in treatment of bipolar disorders, 711–712
- Motivation in children with ADHD, psychostimulants for, 124
- Motor restlessness, as side effect of SSRIs, 266–267

- Movement disorders, as side effect of antipsychotic agents, 377–378
- Nadolol, 576
- Naloxone, 598
- Naltrexone, 598
- Narcolepsy, 113
in children, psychostimulants for, 126–129
- Narcoleptic agents. *See* Antipsychotic agents
- Narcotic-induced side effects of psychostimulants, 134–135
- National Bioethics Advisory Commission (1998), 8
- Nausea, as side effect of clonidine and guanfacine, 563
- Nefazodone, 305–307
dosage and administration, 306
indications for, 305–306
pharmacokinetics, 305
side effects, 306–307
- Nervousness, as side effect of SSRIs, 265
- Net benefit, definition/description of, 59
- Neurally mediated syncope, 93–94
- Neuroleptic malignant syndrome (NMS):
as side effect of antipsychotic agents, 371–372, 376, 378–379
as side effect of lithium, 435–436
as side effect of psychostimulants, 145
- Neuroleptics, 3, 24, 39–40
clonidine or guanfacine for neuroleptic-induced akathisia, 558
- Neurological disorders:
psychoactive drugs interactions in, 651–652
as side effect of lithium, 433–434
- Neuropsychiatric effects of substance abuse, 684–690
acute effects, 684–686
acute neuropsychiatric effects, 686–688
- [Neuropsychiatric effects of substance abuse]
chronic neuropsychiatric effects, 688–690
- Neurotoxicity:
as side effect of CBZ, 461
as side effect of DVP, 466
- Nicotine:
acute neuropsychiatric effects of, 688
cessation of, 692–693
clonidine or guanfacine for nicotine-withdrawal, 556
- Nifedipine, effects on cardiovascular system of, 103
- Nightmares:
as side effect of clonidine and guanfacine, 564
as side effect of propranolol, 585
as side effect of TCAs, 204
- Night terrors:
BZPs for, 515
TCAs for, 193
- Nimodipine, 714
- Nonbenzodiazepine:
chemical structures of, 496
nonbenzodiazepine hypnotics, 494–495, 496
- Nonstimulant medication for ADHD, 24
- Normal cardiac physiology, 88–90
- Nortriptyline:
available preparations and cost of, 208
dosage and regime for ADHD, 182
dosage and regime for enuresis, 184
dosage and regime for MDD, 180
FDA advertising guidelines for, 208
neurotransmitter effects of, 170
- Novel (atypical) antidepressants, 297–316
bupropion, 300–305
mirtazapine, 307–309
nefazodone, 305–307
thyroid hormone, 311–312
trazodone, 297–300
venlafaxine, 309–311

- Nutritional therapy, 602–606
 high-dose vitamin therapy, 603–606
- Obesity:
 opiate antagonists for, 601
 psychostimulants for, 129
- Obsessive-compulsive disorder (OCD):
 BZP for, 506–507
 combination pharmacotherapy for, 716
 lithium for, 430
 SSRIs for, 234–243, 247
 TCAs for, 187–191
 treatment-refractory OCD patients, 243–248
- Ocular irritation, as side effect of lithium, 434
- Olanzapine, 393–395
 available preparations and average cost of, 385
- Omega-3 fatty acids, 621–622
- Opiate antagonists, 597–602
- Opiates:
 acute neuropsychiatric effects of, 687
 chronic neuropsychiatric effects of, 688
- Opioid withdrawal, clonidine or guanfacine for, 556
- Opium, 1, 597–598
- Opportunity cost, definition/description of, 59
- Oral naltrexone. *See* Naltrexone
- Oregon Adolescent Depression Project (OADP), 682
- Organic brain disease in children with ADHD, psychostimulants for, 132–133
- Organ transplantation, adverse psychoactive drug reactions to, 663–664
- Orthostatic (postural) hypotension, 93–94
 as side effect of trazadone, 299–300
- Overdose:
 of antipsychotic agents, 381
 of anxiolytics, 523
 of beta-blockers, 585
- [Overdose]
 of CBZ or DVP, 469
 of clonidine or guanfacine, 565–566
 of lithium, 436–437
 of MAOIs, 342
 of psychostimulants, 145–146
 of SSRIs, 272–273
 of TCAs, 204–206
- Oxazepam, 510
- Pain, adverse psychoactive drug reactions to, 666–667
- Panel on Cost Effectiveness in Health and Medicine, guidelines on CEA, 53–54
- Panic disorders:
 BZP for, 500–502
 clonidine or guanfacine for, 557
 MAOIs for, 330
 propranolol for, 579
 SSRIs for, 252–254
 TCAs for, 187
- Parasomnias, BZPs for, 514–516
- Parenteral naloxone. *See* Naloxone
- Parochial schools, stimulant treatment for ADHD in, 32
- Paroxetine:
 available preparations and cost of, 275
 clinical profile of, 225
 dosage and administration, 278–279
 half-life and metabolic pathways, in OCD treatment, 247
 indications for, 231
 molecular structure, 227
 pharmacokinetics, 229
- Pediatrics:
 antipsychotic agents in pediatric medicine, 370–371
 dosage and administration of SSRIs in pediatric neuropsychiatric conditions, 278–279, 280
 nonpsychiatric pediatric indications for neuroleptic drugs, 361

- [Pediatrics]
- pediatric autoimmune neuropsychiatric disorders associated with GABHS infections, 248–260
 - See also* Ethical issues in pediatric psychopharmacology research
- Pemoline (magnesium pemoline), 24, 113, 156–157
- available preparations and cost of, 149
 - dosage ranges, 152
 - molecular structure, 116
 - pharmacokinetics, 115, 117
 - psychostimulant properties, 158
- Performance anxiety, propranolol for, 578–579
- Perphenazine:
- available preparations and average cost of, 384
 - clinical potency, 357
 - nonpsychiatric pediatric indications for, 361
- Personality disorders:
- antipsychotic agents for, 364–365
 - lithium for, 430–431
- Pervasive development disorder (PDD):
- antipsychotic agents for, 367–369, 380
 - in children with ADHD, psychostimulants for, 132
 - combination pharmacotherapy for, 716
 - opiate antagonists for, 599–600
 - TCA for, 192–193
- Pharmaceutical Research and Manufacturers of America (PRMA), 55
- Pharmacoeconomics research, 51–69
- childhood mental disorders costs, contextual influences, and cost applications, 65–66
 - glossary of terms used in health economics, pharmacoeconomics, and quality of life analysis, 58–59
 - pharmacoeconomic analyses, 54–65
 - costs, perspective, and sensitivity analysis, 57–64
 - types of studies, 56–57
- Pharmacogenetics of drug metabolism, 74–77
- Pharmacokinetic drug-drug interactions, 654–655, 656–660
- Pharmacological concepts relevant to SUDs, 683–684
- Phenelzine, chemical structure of, 319
- Phenobarbital, side effects of, 470
- Phenytoin:
- available preparations and cost of, 474
 - side effects, 470
- Pimozide:
- available preparations and average cost of, 385
 - clinical potency, 357
 - common side effects, 358
 - psychiatric indications and approved age ranges for, 360
- Placebo-controlled clinical trials in child psychopharmacology, 12–13
- Posttraumatic stress disorder (PTSD):
- BZP for, 505–506
 - clonidine or guanfacine for, 558
 - mirtazapine for, 308
 - propranolol for, 578
 - SSRIs for, 259–260
 - TCA for, 194
- Prader-Willi syndrome (PWS), SSRIs for, 258–259
- Prazepam, 510
- Pregnancy:
- adverse psychoactive drug reactions to, 669–670
 - antipsychotic agents and, 372–373
 - clonidine or guanfacine and, 560
 - lithium and, 431
 - psychostimulants and, 136
 - SSRIs and, 261–262
 - TCA and, 195–196
- Premature systoles, 89
- Premenstrual dysphoric disorder (PMDD), SSRIs for, 254–255
- Prepubertal depression, adolescent depression versus, 172
- Preschool children:
- ADHD in, 129–130

- [Preschool children]
 - increase in psychotropic medications for (U.S.—1990s), 3–4
- Prescription data on ATD treatment of adolescents, 36
- Priapism, as side effect of trazadone, 299
- Private schools, stimulant treatment for ADHD in, 32
- Prochlorperazine:
 - available preparations and average cost of, 384
 - clinical potency, 357
 - nonpsychiatric pediatric indications for, 361
 - psychiatric indications and approved age ranges for, 360
- Promethazine:
 - nonpsychiatric pediatric indications for, 361
- Propranolol:
 - available preparations and cost of, 585, 586
 - comparison with other beta-blockers, 576
 - molecular structure, 576
 - pharmacokinetics, 546, 576
- Prozac, parent information of, 277
- Psychiatric consultation-liaison. *See* Psychopharmacology in the physically ill child and adolescent
- Psychiatric disorders in conjunction with SUDs, 695–700
 - ADHD, 696–699
 - aggressive behavior, 699–700
 - bipolar disorders, 696
 - depression and mood disorders, 695–696
 - psychosis, 700
- Psychiatric indications for MAOIs, 324
- Psychoactive drugs, clinical pharmacology of. *See* Clinical pharmacology of psychoactive drugs
- Psychopharmacology for children and adolescents, historical perspective on. *See* Historical perspective
- Psychopharmacology in the physically ill child and adolescent, 635–678
 - comorbidity of physical and psychiatric disorders, 636–639
 - common clinical problems, 660–670
 - cachexia, wasting, and fatigue, 665–666
 - delirium, 660–663
 - HIV/AIDS, 664–665
 - migraine, 667–668
 - pain, 666–667
 - pregnancy and premenstrual disorders, 669–670
 - somatization and somatoform disorders, 668–669
 - transplantation, 663–664
 - consultation and assessment, 639–642
 - principles of management in the physically ill child, 642–660
- Psychosis:
 - in adolescents with SUDs, 700
 - clonidine or guanfacine for, 557
 - lithium for, 426–427
 - psychostimulants contraindicated for, 135–136, 144
 - as side effect of TCAs, 202
- Psychostimulants, 24–35, 113–168, 635
 - abuse, 146–147
 - available preparations and cost of, 149
 - chemical properties, 118–119
 - clinical efficacy, 123–135
 - in concomitant psychotropic medication, 40–41
 - contraindications, 135–140
 - drug interactions with, 147–148
 - effects on cardiovascular system of, 98
 - indications for, 119–123
 - initiating and maintaining treatment, 148–150
 - overdose, 145–146
 - side effects, 140–145
 - specific agents and indications, 149–159
 - dextroamphetamine/adderall, 153–156

- [Psychostimulants]
 - methylphenidate, 149–153
 - pemoline, 156–157
 - youths receiving stimulant medication in U.S. (1974–1998), 23–24
- Psychotropic medication, 23–50
 - cardiac side effects in children, 87–117
 - congenital heart disease, 90
 - congenital long QT syndrome, 90–92
 - drugs used and their effects on cardiovascular system, 98–103
 - guidelines to avoid side effects, 102–104
 - heart rate or heart period variability, 94–95
 - management, 104
 - mitral valve prolapse, 92–93
 - QT dispersion, 95
 - QT variability, 96–97
 - special risks of drug interactions, 103
 - sudden death and psychotropics, 97–98
 - syncope, 93–94
 - ventricular arrhythmias in normal hearts, 92
 - in preschoolers, 3
 - in youth, 23–50
 - α -agonists, 38–39
 - antidepressants, 35–38
 - concomitant psychotropic medication treatment, 40–41
 - neuroleptics, 39–40
 - psychotropic medication prevalence increase in youth treatment (1987–1996), 42
 - stimulants, 24–35
- Public schools, stimulant treatment for ADHD in, 32
- Pulmonary disease, psychoactive drugs interactions in, 649–651
- QT dispersion, 95
- QT variability, 96–97
- Quality-adjusted life year (QALY), 57
- Quality of life analysis, glossary of terms used in, 58–59
- Quazepam, 510
 - major metabolic pathways of, 492
 - sleep response to, 511
- Quetiapine, 391–393
 - available preparations and average cost of, 385
- Race/ethnicity:
 - α -agonist patterns and, 39
 - ATD medication patterns and, 37
 - stimulant prevalence for ADHD and, 28
- Rash:
 - as side effect of SSRIs, 270
 - as side effect of TCAs, 204
- Rebound hypertension, as side effect of clonidine and guanfacine, 563–564
- Rehabilitation Act of 1973 (Section 504), 33
- REM behavior disorder, BZPs for, 515–516
- Renal disease (renal dysfunction):
 - clonidine or guanfacine contraindicated for, 559
 - lithium contraindicated for, 431, 434
 - psychoactive drugs interactions in, 647
- Respiratory sinus arrhythmia (RSA), 88
- Retinal degeneration, as side effect of clonidine and guanfacine, 564
- Reynaud's phenomenon:
 - as side effect of clonidine, 565
 - as side effect of propranolol, 583
- Risperidone, 24, 395–400
 - available preparations and average cost of, 385
- Ritalin. *See* Methylphenidate (Ritalin)
- St. John's wort (*Hypericum perforatum*), 610–613
 - SSRIs contraindicated for, 260

- Schizophrenia:
 antipsychotic agents for, 359–361
 managing side effects, 383–386
 high-dose vitamin therapy for, 604
 propranolol for, 580–581
- School absenteeism/school phobia:
 BZP for, 502–503
 TCAs for, 185–187
- Seasonal affective disorder (winter depression), propranolol for, 58
- Secretin, autism and, 606–607
- Sedation:
 as side effect of clonidine and guanfacine, 560–562
 as side effect of DVP, 466
 as side effect of SSRIs, 265–266
 as side effect of trazadone, 300
- Sedatives (hypnotics):
 acute neuropsychiatric effects of, 687
 chronic neuropsychiatric effects of, 688
- Seizures:
 psychostimulants contraindicated for, 140, 145
 as side effect of bupropion, 302–303
 as side effect of SSRIs, 270
 as side effect of TCAs, 202
- Selective mutism, SSRIs for, 251
- Selective serotonin reuptake inhibitors (SSRIs), 4, 77, 169, 223–296, 633, 712
 abuse, 273
 available preparations, 273, 275
 chemical properties, 224–230
 contraindications, 260–262
 drug interactions with, 273, 274
 effects on cardiovascular system of, 99–100
 indications for, 230–243
 initiating and maintaining treatment, 273–280
 OCD therapy for, 716
 overdose/toxicity, 272–273
 pediatric autoimmune neuropsychiatric disorders associated with GABHS infections, 248–260
- [Selective serotonin reuptake inhibitors (SSRIs)]
 side effects, 262–272
 treatment-refractory OCD patients, 243–248
- Self-injurious behavior (SIB):
 antipsychotic agents for, 369–370
 opiate antagonists for, 599
 SSRIs and, 255–256, 267–268
- Sensitivity analysis, definition/description of, 59
- Separation anxiety:
 BZP for, 502–503
 TCAs for, 185–187
- Serotonergic syndrome, as side effect of MAOIs, 341, 345
- Sertraline, 71, 224
 available preparations and cost of, 275
 clinical profile, 225
 dosage and administration of, 278
 half-life and metabolic pathways, in OCD treatment, 247
 indications for, 231
 molecular structure, 226
 pharmacokinetics, 229
- Sexual dysfunction:
 as side effect of clonidine and guanfacine, 565
 as side effect of SSRIs, 267
 as side effect of TCAs, 204
- Sexual impotence, as side effect of propranolol, 583
- Side effects:
 of anticonvulsants, 469–470
 of antipsychotic agents, 373–381
 of anxiolytics, 520–524
 of bupropion, 302–303
 of clozapine, 391
 of clonidine and guanfacine, 560–565
 of ginkgo, 614
 of ginseng, 617
 of inositol, 621
 of kava kava, 615
 of lithium, 432–438
 of MAOIs, 336–341

- [Side effects]
 - management of specific side effects, 344–345
 - of melatonin, 618–619
 - of mirtazapine, 308–309
 - of nefazodone, 306–307
 - of olanzapine, 394–395
 - of omega-3 fatty acids, 623
 - of opiate antagonists, 601–602
 - of phenobarbital, 470
 - of phenytoin, 470
 - of propranolol, 582–585
 - of psychostimulants, 140–145
 - of quetiapine, 392–393
 - of risperidone, 399
 - of SAME, 620
 - of SSRIs, 262–272
 - of St. John's wort, 612–613
 - of TCAs, 197–204
 - of thyroid hormones, 312
 - of trazadone, 299–300
 - of valerian, 616
 - of venlafaxine, 311
 - of ziprasidone, 401
- Sinus bradycardia, 88
- Skin irritation/disease:
 - clonidine skin patch for, 560
 - as side effect of CBZ, 462
 - as side effect of clonidine and guanfacine, 564
- Sleep problems:
 - clonidine or guanfacine for, 555
 - See also* Insomnia; Nightmares; Night terrors; Somnambulism; Vivid dreams
- Social anxiety disorder:
 - BZP for, 507
 - clonidine or guanfacine for, 558
 - propranolol for, 578–579
- Social interactions in children with ADHD, psychostimulants for, 124
- Social phobias:
 - MAOIs for, 330–331
 - social isolation as side effect of psychostimulants, 142
- Societal perspective for CEA, 61–63
- Sodium depletion, lithium contraindicated for, 432
- Sodium valproate, effects on cardiovascular system of, 102
- Somatization and somatoform disorders, adverse psychoactive drug reactions to, 668–669
- Somnambulism, TCAs for, 193
- Special education, stimulant treatment for ADHD and, 32–33
- Special experimental designs in child psychopharmacology trials, ethical issues involved in, 13–15
- SSRIs. *See* Selective serotonin reuptake inhibitors (SSRIs)
- Stimulants. *See* Psychostimulants
- Stomachache, as side effect of clonidine and guanfacine, 563
- Stramonium (anticholinergic agent), 1
- Substance abuse disorders (SUDs), 679–710
 - conceptualization of the disorder, 680–681
 - epidemiology, 581–583
 - lithium for, 429
 - neuropsychiatric effects of substance abuse, 684–690
 - pharmacological concept relevant to the disorders, 683–684
 - practice of psychopharmacology in adolescents with SUDs, 701–702
 - psychostimulants contraindicated for, 136–137
 - safety and compliance, 700–701
 - TCAs for, 192
 - treatment of comorbid psychiatric disorders, 695–700
 - treatment strategies, 690–698
- Substitution therapy, as SUDs treatment, 692
- Sudden death:
 - antipsychotic agents and, 380
 - psychotropics in children and, 97–98
 - TCAs and, 198–202

- Surgeon General's Call to Action to Prevent Suicide (1999), 52
- Surgeon General's Conference on Children's Mental Health (2000), 52
- Sweating, excess of, as side effect of SSRIs, 265
- Syncope, 93–94
- Tachycardia, 88, 89
as side effect of psychostimulants, 143–144
- Tardive dyskinesia:
beta-blockers for, 581
nonneuroleptic causes of, 377
- TCAs. *See Tricyclic antidepressants (TCAs)*
- Temazepam, 510
- Theophylline, 77
- Thiazide diuretics, 432
- Thiethylperazine, 361
- Thioridazine:
available preparations and average cost of, 384
clinical potency, 357
potency for common side effects, 358
psychiatric indications and approved age ranges for, 360
- Thiothixene:
available preparations and average cost of, 385
clinical potency, 357
potency for common side effects, 358
- Thyroid dysfunction:
lithium contraindicated for, 432
TCAs contraindicated for, 196
- Thyroid hormone therapy, 311–313, 607–609, 714–715
chemical properties, 311
contraindications, 312
dosage and administration, 312
indications for, 312
side effects, 312
- Thyroxine, 714
- Tic disorders:
in children with ADHD, psychostimulants for, 133–134
- [Tic disorders]
combination pharmacotherapy for, 715–716
psychostimulants contraindicated for, 137
as side effect of TCAs, 204
SSRIs for, 250–251
See also Tourette's syndrome
- Tiredness, as side effect of propranolol, 583
- Tobacco (nicotine):
acute neuropsychiatric effects of, 688
cessation of, 692–693
clonidine or guanfacine for nicotine-withdrawal, 556
- Topiramate, 477–479
- Torsades de pointes (TDP), 90
- Tourette's syndrome:
antipsychotic agents for, 365–367
managing side effects, 386
in children with ADHD, psychostimulants for, 133–134
clonidine or guanfacine for, 545–551, 568, 573
combination pharmacotherapy for, 715–716
psychostimulants contraindicated for, 137, 143
SSRIs for, 250–251
- Toxicity:
of beta-blockers, 585
of CBZ or DVP, 469
of lithium, 436–437
of SSRIs, 272–273
- Transient psychotic symptoms, antipsychotic agents for, 364–365
- Tranlycypromine, chemical structure of, 319
- Trazdone, 297–300
chemical properties, 298
dosage and administration, 300
drug interactions with, 300
effects on cardiovascular system of, 100
FDA advertising guidelines for, 208
indications for, 298–299

- [Trazdone]
 neurotransmitter effects of, 170
 side effects, 299–300
 “Treatment as usual” (TIA), ethical issues involved in, 13
- Tremor:
 as side effect of DVP, 466
 as side effect of TCAs, 204
- Triazolam, 510
- Trichotillomania:
 SSRIs for, 256
 TCAs for, 194
- Tricyclic antidepressants (TCAs), 4, 88, 169–222
 abuse, 206
 available preparations and cost, 206, 208
 chemical properties, 170–171
 contraindications, 195–196
 drug interactions, 206, 207
 effects on cardiovascular system of, 98–99
 for enuresis, 36
 indications for, 171–195
 initiating and maintaining treatment, 206–211
 lithium augmentation efficacy of, 712–714
 overdose, 204–206
 side effects, 197–204
- Trifluoperazine:
 available preparations and average cost of, 384
 clinical potency, 357
 potency for common side effects, 358
 psychiatric indications and approved age ranges for, 360
- Trimethobenzamide, nonpsychiatric pediatric indications for, 361
- Tyramine pressor effect, MAOIs and, 340
- Undifferentiated attention deficit disorder, psychostimulants for, 130
- Unipolar depression:
 lithium for, 425–426
 MAOIs for, 326–327
 thyroid hormone therapy for, 607–608
- United States (U.S.):
 children and adolescents with diagnosable mental disorders in (1989), 3
 increase in psychotropic medications for preschoolers in (1990s), 3–4
- Valerian (*Valeriana officinalis*), 615–616
- Valproic acid:
 available preparations and cost of, 474
 contraindications, 460
 drug interactions with, 473
 side effects, 465
- Venlafaxine, 309–311
 dosage and administration, 310–311
 indications for, 309–310
 side effects, 311
- Ventricular arrhythmia, 88
 in normal hearts, 92
- Verapamil, 72
 effects on cardiovascular system of, 103
- Vivid dreams:
 as side effect of clonidine and guanfacine, 564
 as side effect of propranolol, 585
- Vomiting, as side effect of clonidine and guanfacine, 563
- Wasting, adverse psychoactive drug reactions to, 665–666
- Water intoxication, as side effect of CBZ, 464
- Web sites for bioethics resources, 11
- Weight gain:
 as side effect of antipsychotic agents, 379–380

- [Weight gain]
 - as side effect of DVP, 467
 - as side effect of lithium, 435
 - See also* Obesity
- Weight loss:
 - as side effect of psychostimulants, 142
 - as side effect of SSRIs, 264–265
- White House Conference on Mental Health (1999), 52
- Willingness-to-pay approach to health economics, 61–62
- Winter depression, propranolol for, 58
- Withdrawal seizure, as side effect of DVP, 468–469
- Withdrawal symptoms of substance abusers, 691–692
- Youth Risk Behavior Surveillance System (YRBSS), 681, 682
- Ziprasidone, 400–403

